

201-15167B1

Appendix I

Sulfolene

I U C L I D

Data Set

RECEIVED
OPPT ORIO
04 APR 12 PM 12:49

Existing Chemical	: ID: 77-79-2
CAS No.	: 77-79-2
EINECS Name	: 2,5-dihydrothiophene 1,1-dioxide
EINECS No.	: 201-059-7
Molecular Formula	: C4H6O2S
Producer Related Part	
Company	: Chevron Phillips Chemical Company LP
Creation date	: 13.11.2003
Substance Related Part	
Company	: Chevron Phillips Chemical Company LP
Creation date	: 13.11.2003
Memo	:
Printing date	: 23.12.2003
Revision date	:
Date of last Update	: 23.12.2003
Number of Pages	: 47
Chapter (profile)	: Chapter: 1, 2, 3, 4, 5, 7
Reliability (profile)	: Reliability: without reliability, 1, 2, 3, 4
Flags (profile)	: Flags: without flag, confidential, non confidential, WGK (DE), TA-Luft (DE), Material Safety Dataset, Risk Assessment, Directive 67/548/EEC, SIDS

1. General Information

Id 77-79-2
Date 23.12.2003

1.0.1 OECD AND COMPANY INFORMATION

Type : other
Name : Chevron Phillips Chemical Company LP
Partner :
Date :
Street : 10001 Six Pines Drive
Town : 77380 The Woodlands, Texas
Country : United States
Phone :
Telefax :
Telex :
Cedex :
21.11.2003

1.0.2 LOCATION OF PRODUCTION SITE

1.0.3 IDENTITY OF RECIPIENTS

1.1 GENERAL SUBSTANCE INFORMATION

1.1.0 DETAILS ON TEMPLATE

1.1.1 SPECTRA

1.2 SYNONYMS

1-thia-3-cyclopentene 1,1-dioxide
13.11.2003

3-Sulfolene
13.11.2003

butadiene sulfone
13.11.2003

Sulfolene
13.11.2003

1.3 IMPURITIES

1.4 ADDITIVES

1.5 QUANTITY

1. General Information

Id 77-79-2
Date 23.12.2003

1.6.1 LABELLING

1.6.2 CLASSIFICATION

1.7 USE PATTERN

1.7.1 TECHNOLOGY PRODUCTION/USE

1.8 OCCUPATIONAL EXPOSURE LIMIT VALUES

1.9 SOURCE OF EXPOSURE

1.10.1 RECOMMENDATIONS/PRECAUTIONARY MEASURES

1.10.2 EMERGENCY MEASURES

1.11 PACKAGING

1.12 POSSIB. OF RENDERING SUBST. HARMLESS

1.13 STATEMENTS CONCERNING WASTE

1.14.1 WATER POLLUTION

1.14.2 MAJOR ACCIDENT HAZARDS

1.14.3 AIR POLLUTION

1.15 ADDITIONAL REMARKS

1.16 LAST LITERATURE SEARCH

1.17 REVIEWS

1.18 LISTINGS E.G. CHEMICAL INVENTORIES

2.1 MELTING POINT

Value : = 63 - 65.5 ° C
Sublimation :
Method : other: not reported
Year :
GLP : no data
Test substance : other TS

Source : The Merck Index (O'Neil, 2001, 13th ed.) and the Industrial Solvents Handbook (Flick, 1985, 3rd ed.)

Test substance : 2,5-dihydrothiophene 1,1-dioxide [CAS 77-79-2]

Reliability : (2) valid with restrictions
Flag : Critical study for SIDS endpoint
26.11.2003 (6) (21)

Value : = 17.4 ° C
Sublimation :
Method : other: EPIWIN v 3.10
Year : 2003
GLP : no
Test substance : other TS

Method : EPIWIN v 3.10 - Selected Melting Point, Mean Value.

Source : EPI Suite v 3.10

Test substance : Thiophene, 2,5-dihydro-, 1,1-dioxide or Sulfolene (CAS Number 77-79-2)

Reliability : (2) valid with restrictions
Flag : Critical study for SIDS endpoint
25.11.2003 (25)

2.2 BOILING POINT

Value : = 201.1 ° C at
Decomposition :
Method : other: EPIWIN v 3.10
Year : 2003
GLP : no
Test substance : other TS

Method : EPIWIN v 3.10 - Adapted Stein and Brown Method

Source : EPI Suite v 3.10

Test substance : Thiophene, 2,5-dihydro-, 1,1-dioxide or Sulfolene (CAS Number 77-79-2)

Reliability : (2) valid with restrictions
Flag : Critical study for SIDS endpoint
25.11.2003 (25)

Decomposition : yes
Method : other: not reported
Year :

2. Physico-Chemical Data

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GLP : no data
Test substance : other TS

Remark : This substance decomposes above melting point

Source : Industrial Solvents Handbook (Flick, 1985, 3rd ed.) and Hawley's Condensed Chemical Dictionary (Lewis, 2001, 14th ed.)

Test substance : 2,5-dihydrothiophene 1,1-dioxide [CAS 77-79-2]

Reliability : (2) valid with restrictions
Flag : Critical study for SIDS endpoint
26.11.2003

(6) (17)

2.3 DENSITY

2.3.1 GRANULOMETRY

2.4 VAPOUR PRESSURE

Value : = .175986 hPa at 25° C
Decomposition :
Method : other (calculated): EPIWIN v 3.10
Year : 2003
GLP : no
Test substance : other TS

Method : EPIWIN v 3.10 - Selected Vapor Pressure (Modified Grain Method) using a boiling point of 201.11 deg C and a melting point of 65 deg C.

Result : Selected Vapor Pressure = 0.132 mm Hg (at 25 deg C). When converted to hPa, Vapor Pressure = 0.175986 hPa.

Source : EPI Suite v 3.10

Test substance : Thiophene, 2,5-dihydro-, 1,1-dioxide or Sulfolene (CAS Number 77-79-2)

Reliability : (2) valid with restrictions
Flag : Critical study for SIDS endpoint
25.11.2003

(25)

2.5 PARTITION COEFFICIENT

Log pow : = - 0.8
Method : other (calculated): fragment contribution calculation method
Year : 1983
GLP : no
Test substance : other TS

Method : Calculation of log Pow using the structural data file MACCS. The log Pow value was calculated from chemical structure using the fragment-addition method of Hansch and Leo (1979). An IMLAC (or VT/100) console with a light pen system was used to run the structural data file MACCS. An associated programme (CLOG P. REV 2.1) connected with this structural file enables calculation of log Pow. The programme is limited in that it

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cannot handle any ionic, inorganic or organometallic compounds. Also, two of the correction factors, i.e. ring cluster and intramolecular hydrogen bonding, cannot be perceived and calculated. Further details of the capabilities, design and structure of this programme are provided elsewhere (Chou and Jurs, 1979).

Remark	: Results indicate a low hydrophobicity and low potential for Sulfolene to accumulate from water into organisms. (author)
Source	: TSCA Section 8 (D) Health and Safety Data Reporting, Shell Oil Company submission. Study title: Sulfolene: Acute Toxicity (<i>Salmo gairdneri</i> , <i>Daphnia magna</i> , and <i>Selenastrum capricornutum</i>), and N-Octanol/Water Partition Coefficient. (Experiment Number 2733). Testing Facility: Sittingbourne Research Centre, Sittingbourne, Kent.
Test substance	: Sulfolene obtained from Shell Chemicals U.K. Ltd. Sample contained 7% isopropyl alcohol.
Reliability Flag 26.11.2003	: (1) valid without restriction : Critical study for SIDS endpoint (2) (7) (27)
Log pow	: < 1
Method	other (measured): reverse-phase HPLC
Year	: 1983
GLP	: no
Test substance	: other TS
Method	: Method described by Eadsforth (1982). The HPLC system used was a reverse-phase C18-coated silica gel column (Partisil ODS-3), 250 mm x 5 mm id, with a mobile phase of 3 volumes methanol and 1 volume water (final pH 6.7) at a flow rate of 1 ml/min. Samples (25 ul) of an approximate 1 mg/ml solution in the above mobile phase were injected and the emergence of the material determined using refractive index detection. From the retention time of the peak the log Pow value was determined.
Remark	: Results indicate a low hydrophobicity and low potential for Sulfolene to accumulate from water into organisms. (author)
Source	: TSCA Section 8 (D) Health and Safety Data Reporting, Shell Oil Company submission. Study title: Sulfolene: Acute Toxicity (<i>Salmo gairdneri</i> , <i>Daphnia magna</i> , and <i>Selenastrum capricornutum</i>), and N-Octanol/Water Partition Coefficient. (Experiment Number 2733). Testing Facility: Sittingbourne Research Centre, Sittingbourne, Kent.
Test substance	: Sulfolene obtained from Shell Chemicals U.K. Ltd. Sample contained 7% isopropyl alcohol.
Reliability Flag 26.11.2003	: (1) valid without restriction : Critical study for SIDS endpoint (5) (27)
Log pow	: = - 0.45
Method	other (calculated): EPIWIN v 3.10
Year	: 2003
GLP	: no
Test substance	: other TS
Method	: EPIWIN v 3.10 - Log Kow used by Water solubility estimates.
Source	: EPI Suite v 3.10

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Date 23.12.2003

Test substance : Thiophene, 2,5-dihydro-, 1,1-dioxide or Sulfolene (CAS Number 77-79-2).

Reliability : (2) valid with restrictions

Flag : Critical study for SIDS endpoint

25.11.2003

(25)

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2.6.1 WATER SOLUBILITY

Value : = 5.9 wt% at 25 ° C

Qualitative :

Pka :

PH :

Method : other: measured, method not reported

Year :

GLP : no data

Test substance : other TS

Source : Industrial Solvents Handbook (Flick, 1985, 3rd ed.)

Test substance : 2,5-dihydrothiophene 1,1-dioxide [CAS 77-79-2]

Reliability : (2) valid with restrictions

Flag : Critical study for SIDS endpoint

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(6)

Value : = 287900 mg/l

Qualitative : very soluble (> 10000 mg/L)

Pka :

PH :

Method : other: EPIWIN v 3.10

Year : 2003

GLP : no

Test substance : other TS

Source : EPI Suite v 3.10

Test substance : Thiophene, 2,5-dihydro-, 1,1-dioxide or Sulfolene (CAS Number 77-79-2).

Reliability : (2) valid with restrictions

Flag : Critical study for SIDS endpoint

25.11.2003

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13.11.2003

2.6.2 SURFACE TENSION

2.7 FLASH POINT

2.8 AUTO FLAMMABILITY

2.9 FLAMMABILITY

2. Physico-Chemical Data

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Date 23.12.2003

2.10 EXPLOSIVE PROPERTIES

2.11 OXIDIZING PROPERTIES

2.12 ADDITIONAL REMARKS

3.1.1 PHOTODEGRADATION

Type	: other
Light source	:
Light spect.	: nm
Rel. intensity	: based on Intensity of Sunlight
Deg. Product	:
Method	: other (calculated): EPIWIN v 3.10
Year	: 2003
GLP	: no
Test substance	: other TS
Method	: Calculated using EPIWIN v 3.10 (AOP Program v1.90).
Result	: Ozone Rate Constant = 20 E-17 cm ³ /molecule-sec Ozone Half Life = 1.375 hrs (at 7E11 mol/cm ³) OH Rate Constant = 65.725 E-12 cm ³ /molecule-sec OH Half Life = 1.953 Hrs (12-hr day; 1.5E6 OH/cm ³)
Source	: EPI Suite v 3.10
Reliability	: (2) valid with restrictions
Flag	: Critical study for SIDS endpoint
26.11.2003	(25)

3.1.2 STABILITY IN WATER

3.1.3 STABILITY IN SOIL

3.2 MONITORING DATA

3.3.1 TRANSPORT BETWEEN ENVIRONMENTAL COMPARTMENTS

Type	: fugacity model level III
Media	: other: air - water - soil - sediment
Air (level I)	:
Water (level I)	:
Soil (level I)	:
Biota (level II / III)	:
Soil (level II / III)	:
Method	: other: EPI Suite v 3.10
Year	: 2003
Method	: Level III Fugacity Model (EPI Suites).
	The following physical properties were used as the model input parameters:
	Chem Name: Thiophene, 2,5-dihydro-, 1,1-dioxide
	Molecular Wt: 118.15
	Henry's LC: 4.27E-006 atm-m ³ /mole (Henrywin program)
	Vapor Press: 0.133 mm Hg (Mppwin program)
	Log Kow: -0.45 (Kowwin program)
	Soil Koc: 0.145 (calc by model)
Result	: Results are provided in the following format: Compartment / 100% to Air / 100% to Water / 100% to Soil / Equally to

3. Environmental Fate and Pathways

Id 77-79-2
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Each Compartment

Air / 69.6% / 0.006% / 0.03% / 0.2%
Water / 16.7% / 99.8% / 21.7% / 55.9%
Soil / 13.7% / 0.001% / 78.2% / 43.8%
Sediment / 0.03% / 0.167% / 0.04% / 0.1%

Air: half life = 1.017 hr; emissions = 1000 kg/hr
Water: half life = 360 hr; emissions = 1000 kg/hr
Soil: half life = 360 hr; emissions = 1000 kg/hr
Sediment: half life = 1440 hr; emissions = 0 kg/hr

Persistence when distributed equally to each compartment = 257 hr
(Emissions [kg/hr] = 1000 to air, 1000 to water, 1000 to soil, and 0 to sediment)

Source : EPI Suite v 3.10

Test substance : Thiophene, 2,5-dihydro-, 1,1-dioxide or Sulfolene (CAS Number 77-79-2).

Reliability : (2) valid with restrictions
Flag : Critical study for SIDS endpoint
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3.3.2 DISTRIBUTION

3.4 MODE OF DEGRADATION IN ACTUAL USE

3.5 BIODEGRADATION

Type : aerobic
Inoculum : other: Micro-organisms were obtained from Canterbury Sewage Works and prepared according to the prescribed methods for this test.
Concentration : 20mg/l related to Test substance
related to
Contact time : 28 day
Degradation : = 2 % after 28 day
Result : other: not readily biodegradable
Control substance : Benzoic acid, sodium salt
Kinetic : 5 day > 50 %
15 day > 75 %
Deg. Product : not measured
Method : OECD Guide-line 301 B "Ready Biodegradability: Modified Sturm Test (CO2 evolution)"
Year : 1984
GLP : no data
Test substance : other TS

Result : Only 2% of the theoretically possible carbon dioxide was evolved by 28 days. According to the OECD guideline 301, the test substance cannot be considered as readily biodegradable.

Source : TSCA Section 8 (D) Health and Safety Data Reporting, Shell Oil Company submission. Study title: Sulfolene: An Assessment of Ready Biodegradability. Testing Facility: Sittingbourne Research Centre, Sittingbourne, Kent.

3. Environmental Fate and Pathways

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Test condition	: Sulfolene was added to the test medium from a stock solution containing 1 g/l to give a final test concentration of 20 mg/l sulfolene. The test medium was dispensed into the Sturm vessels, inoculated and aerated with 60 ml/min of CO ₂ -free air at 25 +/- 1 deg. C. The extent of biodegradation at 1, 4, 7, 12, 19, 22, 26, and 28 days was determined by titrating the total carbon dioxide released from the incubation. The medium was acidified on day 27 to release the total carbon dioxide by day 28. INOCULUM: Micro-organisms were obtained from Canterbury Sewage Works and prepared according to the prescribed methods for this test. CONTROLS: Positive Control: Sodium benzoate was used as a degradable substance to demonstrate the activity of the microbial inoculum. Control: Mineral medium Blank: Microbial inoculum
Test substance	: Approximately 90% sulfolene (2,5-dihydrothiophene 1,1-dioxide) and 7% isopropyl alcohol
Reliability Flag 26.11.2003	: (1) valid without restriction : Critical study for SIDS endpoint (28)
Type Inoculum	: aerobic : other: Micro-organisms were obtained from Canterbury Sewage Works and prepared according to the prescribed methods for this test.
Concentration	: 3mg/l related to Test substance related to
Contact time	: 28 day
Degradation	: = 0 % after 28 day
Result	: other: Not readily biodegradable
Control substance	: Benzoic acid, sodium salt
Kinetic	: 5 day > 60 %
Deg. Product Method Year	: : OECD Guide-line 301 D "Ready Biodegradability: Closed Bottle Test" : 1984
GLP	: no data
Test substance	: other TS
Remark	: Sulfolene did not inhibit microbial activity in the Closed Bottle test, although some inhibition of the growth of Pseudomonas fluorescens was found in a separate test, 50% inhibition was not achieved even at a concentration of 1000 mg/l sulfolene.
Result	: According to the OECD guideline 301, the test substance cannot be considered as readily biodegradable
Source	: TSCA Section 8 (D) Health and Safety Data Reporting, Shell Oil Company submission. Study title: Sulfolene: An Assessment of Ready Biodegradability. Testing Facility: Sittingbourne Research Centre, Sittingbourne, Kent.
Test condition	: TEST DESIGN -Sulfolene was added to the test medium from a stock solution of 1 g/l to give a final test concentration of 3 mg/l sulfolene. -The bottles were incubated at 20 +/- 1 deg C and the extent of biodegradation determined by measuring the oxygen concentration in the bottles at 5, 15, and 28 days.

3. Environmental Fate and Pathways

Id 77-79-2
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INOCULUM/TEST ORGANISM: Micro-organisms were obtained from Canterbury Sewage Works and prepared according to the prescribed methods for this test.

CONTROLS

Positive control: Sodium Benzoate

Control: Mineral medium

Blank: Microbial inoculum

INTERMEDIATES/DEGRADATION PRODUCTS: Not identified.

Test substance : Approximately 90% sulfolene (2,5-dihydrothiophene 1,1-dioxide) and 7% isopropyl alcohol.

Reliability : (1) valid without restriction
Flag : Critical study for SIDS endpoint
26.11.2003

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3.6 BOD5, COD OR BOD5/COD RATIO

3.7 BIOACCUMULATION

BCF : = 3.16
Elimination :
Method : other: calculated with EPIWIN v 3.10
Year : 2003
GLP : no
Test substance : other TS

Method : Calculated using EPIWIN v 3.10 (BCF Program v 2.14)

The following parameters were used:

Log Kow (estimated): -0.45

Log Kow (experimental): not available from database

Log Kow used by BCF estimates: -0.45

Correction Factors Not Used for Log Kow <1.

Calculated Koc using EPIWIN v 3.10 (PCKOC Program v 1.66)

Result : Estimated Log BCF = 0.500
BCF = 3.162

Estimated Log Koc = 1.3343

Estimated Koc = 21.59

Source : EPI Suite v 3.10

Test substance : Thiophene, 2,5-dihydro-, 1,1-dioxide or Sulfolene (CAS Number 77-79-2).

Reliability : (2) valid with restrictions
26.11.2003

(25)

3.8 ADDITIONAL REMARKS

4.1 ACUTE/PROLONGED TOXICITY TO FISH

Type	: static
Species	: Salmo gairdneri (Fish, estuary, fresh water)
Exposure period	: 96 hour(s)
Unit	: mg/l
Analytical monitoring	: no
LC50	: = 940
Method	: other
Year	: 1983
GLP	: no data
Test substance	: other TS
Method	: Comparable to OECD Guideline 203 and U.S. EPA Guideline 797.1400 (OPPTS 850.1075).
Result	: Cumulative Mortality: Conc. in mg/l / 24hr / 48hr / 72hr / 96hr 0 / 0 / 0 / 0 / 0 100 / 0 / 0 / 0 / 0 200 / 0 / 0 / 0 / 0 500 / 0 / 0 / 0 / 0 1000 / 1 / 4 / 6 / 6 -No concentration caused 100% mortality Mortality of Controls: 0
Source	: TSCA Section 8 (D) Health and Safety Data Reporting, Shell Oil Company submission. Study title: Sulfolene: Acute Toxicity (Salmo gairdneri, Daphnia magna, and Selenastrum capricornutum), and N-Octanol/Water Partition Coefficient. (Experiment Number 2733). Testing Facility: Sittingbourne Research Centre, Sittingbourne, Kent.
Test condition	: TEST ORGANISMS - Rainbow trout, S. gairdneri, Itchen Valley Trout Farm, Alresford, Hampshire - Mean length 3.7 cm (3.3 - 4.1) - Mean weight 0.45 g (0.27 - 0.64) - Measurements from sample 10 fish - Acclimated to test conditions >10 days before test - Number of dead fish recorded at 24 hr intervals DETAILS OF TEST - Static with daily renewal of test solutions DILUTION WATER SOURCE - From laboratory mains supply - From two pumping stations (Newnham and Wychling) controlled by the Mid Kent Water Company. Water is obtained from bore holes in the chalk of the North Downs. - Chemical treatment prior to arrival: chlorination to 0.1 mg/l IN LAB TREATMENT: - Filtered to remove particles larger than 8 um, chlorine, and organic compounds - Stainless steel heat exchange units used to adjust temperature - Aerated for several hours prior to test to remove residual chlorine

DILUTION WATER CHEMISTRY

- Range 13/10/80 - 4/10/83 (n=16)
- pH: 7.1-7.8
- Alkalinity: 253-275
- Hardness: 259-300

VEHICLE/SOLVENT AND CONCENTRATIONS

- Stock solution of Sulfolene in distilled water
- Logarithmic series of 4 concentrations between 100 and 1000 mg/l

NOMINAL TEST CONCENTRATIONS:

- 100 mg/l
- 200 mg/l
- 500 mg/l
- 1000 mg/l

MEASURED CONCENTRATIONS: No data

STABILITY OF THE CHEMICAL SOLUTION: Infra-red spectrum test confirmed substance was Sulfolene after 3 years of storage. On this basis material was considered stable for the duration of the study.

EXPOSURE VESSEL TYPE

- 10 fish in each aquarium
- 10 liters of water

TEST WATER CHEMISTRY

- pH: 7.8-8.5 (Control, 7.6-7.8; Top Concentration, 7.9-8.1)
- Hardness: 250-270 mg/l as CaCO₃
- Dissolved oxygen: 9.6-10.3 mg/l

TEST TEMPERATURE RANGE

- Monitored at 4 hourly intervals by a computer controlled thermocouple system which outputs when temperature deviates more than 2 deg C from nominal
- Range: 13 - 17 deg C for all groups through test

PHYSICAL MEASUREMENTS

- Test temperature: 13 - 17 deg C
- Concentration of dissolved oxygen (mg/L)
 - Control (mg/L):
 - 0 hr = 10.2
 - 24 hr = 9.6/10.0
 - 48 hr = 9.9/10.3
 - 72 hr = 9.7/9.6
 - 96 hr = 9.9
 - Top dose concentration (mg/L):
 - 0 hr = 10.2
 - 24 hr = 9.8/10.1
 - 48 hr = 9.9/10.1
 - 72 hr = 9.9/9.6
 - 96 hr = 9.9

- pH
 - Control:
 - 0 hr = 7.8
 - 24 hr = 8.4/8.2
 - 48 hr = 8.2/8.2
 - 72 hr = 8.2/8.2
 - 96 hr = 8.2
 - Top dose concentration:
 - 0 hr = 8.0

--- 24 hr = 8.5/8.4
 --- 48 hr = 8.3/8.3
 --- 72 hr = 8.3/8.2
 --- 96 hr = 8.2

STATISTICAL METHODS: 96 hr LC50 was estimated by graphical interpolation using log/probit graph paper.

CONTROLS: One aquarium received no Sulfolene and served as a control.

Test substance : Sulfolene (2,5-dihydrothiophene 1,1-dioxide) supplied by Shell Chemicals U.K. Ltd. Sample contained ~ 7% isopropyl alcohol.

Reliability : (1) valid without restriction
Flag : Critical study for SIDS endpoint
 26.11.2003

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4.2 ACUTE TOXICITY TO AQUATIC INVERTEBRATES

Type : static
Species : Daphnia magna (Crustacea)
Exposure period : 48 hour(s)
Unit : mg/l
Analytical monitoring : no
EC50 : = 800
95% fiducial limits : = 690 - 940
EC50, 24 h : > 1000
Method : other
Year : 1983
GLP : no
Test substance : other TS

Method : Comparable to OECD 202 and EPA 797.1330 (OPPTS 850.1300).

Result : Number Immobilized
 Conc in mg/L / 24hr / 48hr
 0 mg/L / 0 / 0
 0 mg/L / 0 / 0
 0 mg/L / 0 / 0

50 mg/L / 0 / 0
 50 mg/L / 0 / 0
 50 mg/L / 0 / 0

100 mg/L / 0 / 0
 100 mg/L / 0 / 0
 100 mg/L / 0 / 0

200 mg/L / 0 / 0
 200 mg/L / 0 / 0
 200 mg/L / 0 / 0

500 mg/L / 0 / 1
 500 mg/L / 0 / 2
 500 mg/L / 0 / 0

1000 mg/L / 2 / 5
 1000 mg/L / 1 / 9

1000 mg/L / 0 / 8

Source : TSCA Section 8 (D) Health and Safety Data Reporting, Shell Oil Company submission. Study title: Sulfolene: Acute Toxicity (Salmo gairdneri, Daphnia magna, and Selenastrum capricornutum), and N-Octanol/Water Partition Coefficient. (Experiment Number 2733). Testing Facility: Sittingbourne Research Centre, Sittingbourne, Kent.

Test condition : TEST ORGANISMS: Daphnia magna, less than 24 hrs old, were taken from a culture in STL derived from a strain obtained (via ICI Brixham Laboratory) from I.R.Ch.A., France.

STABILITY OF THE CHEMICAL SOLUTION: Infra-red spectrum test confirmed substance was Sulfolene after 3 years of storage. On this basis material was considered stable for the duration of the study.

TEST TEMPERATURE RANGE

- Monitored at 4 hourly intervals by a computer controlled thermocouple system which outputs when temperature deviates more than 2 deg C from nominal
- Range: 18-22 deg C for all groups throughout test

EXPOSURE VESSEL

- 100 ml water in 150 ml glass crystallizing dishes
- 10 test animals per dish

WATER

- Water used for culturing and testing was a reconstituted fresh water prepared by dissolving the following amounts of Analar grade salts in glass distilled deionised water:

NaHCO₃ 192 mg/l

CaSO₄*2H₂O 120 mg/l

MgSO₄ 120 mg/l

KCl 8 mg/l

TEST DESIGN

- 3 replicates
- 10 individuals per replicate
- Concentrations: logarithmic series of concentration ranging from 50 to 1000 mg/l:

TEST CONCENTRATIONS:

50 mg/l

100 mg/l

200 mg/l

500 mg/l

1000 mg/l

MEASURED CONCENTRATIONS: No data

IMMOBILIZATION

- Counted and recorded at 24 hr and 48 hr
- D. magna were considered to be immobile if, when the contents of the dish were briefly stirred they did not swim during a 10 minute period of observation.

EXPOSURE PERIOD: 48hr

STATISTICAL METHODS: 48hr EC₅₀ was calculated using probit analysis after log transformation of the concentrations.

CONTROLS: Three dishes served as controls and received no sulfolene.

WATER CHEMISTRY IN TEST

- pH: 7.9-8.0 (for control and top concentration)
- Hardness: 170 mg/l as CaCO₃
- Dissolved oxygen: 8.8-9.0 mg/l (for control and top concentration)

PHYSICAL MEASUREMENTS

- Test temperature: 18 - 22 deg C
- Total hardness: 170 mg/l as CaCO₃
- Concentration of dissolved oxygen (mg/l):
 - Control (mg/l):
 - 0 hr = 9.0
 - 48 hr = 8.8
 - Top dose concentration (mg/l):
 - 0 hr = 9.0
 - 48 hr = 8.8
- pH
 - Control:
 - 0 hr = 8.0
 - 48 hr = 7.9
 - Top dose concentration:
 - 0 hr = 8.0
 - 48 hr = 7.9

Test substance : Sulfolene (2,5-dihydrothiophene 1,1-dioxide) supplied by Shell Chemicals U.K. Ltd. Sample contained ~ 7% isopropyl alcohol.

Reliability : (1) valid without restriction
Flag : Critical study for SIDS endpoint
 26.11.2003

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4.3 TOXICITY TO AQUATIC PLANTS E.G. ALGAE

Species : *Selenastrum capricornutum* (Algae)
Endpoint : growth rate
Exposure period : 4 day
Unit : mg/l
Analytical monitoring : no data
EC50 : > 1000
Method : other
Year : 1983
GLP : no
Test substance : other TS

Method : Comparable to OECD 201 and EPA 797.1050 (OPPTS 850.5400).

Result : Growth of *S. capricornutum* cultures exposed to a range of concentrations of Sulfolene

Cell density at each flask at each measuring point:

(Dose Concentration / Day 2 cell concentration [in cells/ml x 10⁶] / Day 4 cell concentration [in cells/ml x 10⁶])

0 mg/L / 0.013 / 0.47

/ 0.013 / 0.62

/ 0.015 / 0.65

/ 0.013 / 0.57

/ 0.012 / 0.39

/ 0.013 / 0.56

10 mg/L / 0.013 / 0.76

20 mg/L / 0.013 / 0.60
50 mg/L / 0.013 / 0.61
100 mg/L / 0.010 / 0.46
200 mg/L / 0.015 / 0.72
500 mg/L / 0.016 / 0.76
1000 mg/L / 0.013 / 0.73

Cell Number of Day 4 as % Mean Control Cell Number Day 4:

10 mg/l: 139
20 mg/l: 110
50 mg/l: 112
100 mg/l: 84
200 mg/l: 132
500 mg/l: 141
1000 mg/l: 134

Source : TSCA Section 8 (D) Health and Safety Data Reporting, Shell Oil Company submission. Study title: Sulfolene: Acute Toxicity (*Salmo gairdneri*, *Daphnia magna*, and *Selenastrum capricornutum*), and N-Octanol/Water Partition Coefficient. (Experiment Number 2733). Testing Facility: Sittingbourne Research Centre, Sittingbourne, Kent.

Test condition : TEST TEMPERATURE RANGE
- Monitored at 4 hourly intervals by a computer controlled thermocouple system which outputs when temperature deviates more than 2 deg C from nominal
- Range: 22-26 deg C for all groups through test

GROWTH/TEST MEDIUM

- A nutrient medium was prepared by dissolving Analar grade salts in glass-distilled deionised water. Nutrient concentrations were those described by Miller and Green (1978) except that boric acid was present at 105 g/l, and sodium bicarbonate was present at 50 mg/l.
- The medium (excluding sodium bicarbonate) was autoclaved at 1.0 kg/cm² for 15 min. On cooling, 20 ml/l of a millipore-serilized solution of sodium bicarbonate (2.5 g/l) was added.

EXPOSURE VESSEL TYPE: Erlenmeyer flask containing 50 ml of culture medium.

TEST ORGANISM: *S. capricornutum* were taken from a axenic culture in STL derived from a strain (ATCC 22662) obtained from the American Type Culture Collection, Maryland, USA.

TEMPERATURE, pH, AND WATER HARDNESS DURING TEST

- Measured at beginning and end of test
- Temperature: 22 - 26 deg C
- pH
-- Control:
--- 0 hr = 7.7
--- 2 day = 7.6
--- 4 day = 7.8
-- Top concentration:
--- 0 hr = 8.1
--- 2 day = 8.0
--- 4 day = 7.9
- Hardness: 170 mg/l as CaCO₃

LIGHTING

- Constant illumination (~3000 lux)

TEST DESIGN

- 7 flasks containing Sulfolene in distilled water to give logarithmic concentrations from 10 to 1000 mg/l
- 6 control flasks
- *S. capricornutum* 500 cells/ml
- Incubated in a cooled, orbital incubator (100 cycles/min)
- Cell counts after 2 and 4 days using Coulter Counter

Test substance : Sulfolene (2,5-dihydrothiophene 1,1-dioxide) supplied by Shell Chemicals U.K. Ltd. Sample contained ~ 7% isopropyl alcohol.

Reliability : (1) valid without restriction
Flag : Critical study for SIDS endpoint

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4.4 TOXICITY TO MICROORGANISMS E.G. BACTERIA**4.5.1 CHRONIC TOXICITY TO FISH****4.5.2 CHRONIC TOXICITY TO AQUATIC INVERTEBRATES****4.6.1 TOXICITY TO SOIL DWELLING ORGANISMS****4.6.2 TOXICITY TO TERRESTRIAL PLANTS****4.6.3 TOXICITY TO OTHER NON-MAMM. TERRESTRIAL SPECIES****4.7 BIOLOGICAL EFFECTS MONITORING****4.8 BIOTRANSFORMATION AND KINETICS****4.9 ADDITIONAL REMARKS**

5.1.1 ACUTE ORAL TOXICITY

Type	: LD50
Species	: rat
Strain	: Sprague-Dawley
Sex	: male/female
Number of animals	: 55
Vehicle	: no data
Value	: = 2876.1 mg/kg bw
Method	: other
Year	: 1982
GLP	: no data
Test substance	: other TS
Method	: Comparable to OECD 401
Result	<p>: VALUE:</p> <p>LD50 mg/kg (95% confidence interval): Female: 2547.3 (2146.4 - 3023.0) Male: 3006.5 (2440.9 - 3703.2) Combined: 2876.1 (2544.3 - 3251.2)</p> <p>NUMBER OF DEATHS AT EACH DOSE INTERVAL:</p> <p>1000 mg/kg: 0 males, 0 females 2000 mg/kg: 0 males, 0 females 2500 mg/kg: 3 females 3000 mg/kg: 2 males, 5 females 4000 mg/kg: 5 males, 4 females 5000 mg/kg: 5 males, 5 females</p> <p>TIMES OF DEATH:</p> <p>2500 mg/kg: 3 females (1 on day 1, 2 on day 7) 3000 mg/kg: 2 males (1 on day 2, 1 on day 4); 5 females (5 on day 1) 4000 mg/kg: 5 males (1 at hour 4, 4 on day 1); 4 females (2 at hour 4, 2 on day 1) 5000 mg/kg: 5 males (3 at hour 2, 2 on day 1); 5 females (2 at hour 2, 3 on day 1)</p> <p>CLINICAL OBSERVATIONS</p> <ul style="list-style-type: none">- Clinical observations were noted among all rats by one, two, or four hours post dose.- Included: depression, slight depression, rough coat, urine stains, thinness, red stains on nose/eyes, soft feces, a hunched appearance, tremors, salivation, lacrimation, ataxia, prostration, labored respiration, and convulsions.- All rats that survived to termination gained weight.- All rats that died lost weight, with the exception of one that gained weight.- No observable gross pathology was noted in rats surviving to termination.- Alterations of the stomach were most consistent among the animals that died and included: distension of stomach and intestines, compound-like material, dark red material, thick brackish fluid, yellowish fluid, or reddish fluid in the stomach and/or intestines.- Other findings in the lung and liver were considered incidental.
Source	: Phillips Petroleum Company Acute Oral Toxicity Study in Rats - Sulfolene - Final Report. Study performed by Hazleton Laboratories America Inc., Vienna Virginia.
Test condition	: DOSE CONCENTRATIONS: 1000 mg/kg, 2000 mg/kg, 2500 mg/kg, 3000

mg/kg, 4000 mg/kg, 5000 mg/kg

ROUTE OF ADMINISTRATION: Gavage

TEST CONDITIONS:

- Age: young adult (200 - 300 grams).
- Two animals per cage.
- 12 hour light-dark cycle.
- Single dose of test material, animals fasted 18 to 24 hours prior to dosing.
- Group 1 dosed with 5000 mg/kg, results reported after 48 hours indicated need for additional groups to be added to determine LD50.
- 5 male and 5 female rats per dose concentration with the exception of only 5 females (no males) being dosed at 2500 mg/kg.
- Observation of Animals: Day of dosing - 1,2, and 4 hours; twice daily thereafter. Observations include nature, onset, severity, and duration of pharmacotoxic signs.
- Body Weights: Taken just prior to treatment (dosage volume for each rat is based on this weight), at death, and/or at seven and 14 days.
- Post dose observation period: 14 days
- At study termination:
 - Animals that Succumb: Necropsies were performed by appropriately trained personnel under procedures supervised by board-certified pathologist.
 - Sacrifice: At Day 14, all surviving animals were weighed, anesthetized, and exsanguinated. Necropsies were performed by appropriately trained personnel under procedures supervised by board-certified pathologist.

Test substance : Sulfolene (2,5-dihydrothiophene 1,1-dioxide) -- no data on purity.

Reliability : (1) valid without restriction
Flag : Critical study for SIDS endpoint
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5.1.2 ACUTE INHALATION TOXICITY

Type : LC50
Species : rat
Strain : Wistar
Sex : male/female
Number of animals : 10
Vehicle : no data
Exposure time : 4 hour(s)
Method : other
Year : 1980
GLP : no data
Test substance : other TS

Method : Comparable to OECD 403.

Result : LC50: greater than the saturated concentration in air at 25°C. No deaths reported in dose group.

CLINICAL SIGNS: No clinical signs were reported for any dose animals.

NECROPSY FINDINGS

- Macroscopic: Four dose animals had lungs that appeared dark, pale, or patchy at necropsy.
- Microscopic: Focal intra-alveolar haemorrhage and slight alveolar collapse in two of the exposed animals. Evidence of this type was also seen in control rats, and absence of signs of pulmonary irritation lead to

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conclusion that microscopic findings are not treatment induced.

Source : TSCA Section 8 (D) Health and Safety Data Reporting Shell Oil Company submission. Study report entitled "Toxicology of fine chemicals: The acute 4 h inhalation LC50 of sulfolene in rats. Testing facility was Sittingbourne Research Centre, Sittingbourne, Kent.

Test condition : Approximately 99% sulfolene (2,5-dihydrothiophene 1,1-dioxide) and 0.9% isopropyl alcohol

Test substance : NUMBER OF ANIMALS PER SEX PER DOSE GROUP:
5 male/5 female/dose
10 male/10 female/control

AGE: 8-9 weeks

WEIGHT: females 171-204 g, males 285-316 g

EXPOSURE CHAMBERS

- Test animals housed in two 7 litre tubular glass chambers fitted with stainless steel mesh carriers to accomodate five animals each.
- Test atmosphere supplied to each chamber at a minimum flow rate of 10 L/min.
- Chambers located in the fume cupboard together with the atmosphere generator.

ATMOSPHERE GENERATOR: Test atmosphere was generated using a modified version of the wick method.

VOLUME ADMINISTERED: 20 litres of clean dry air per minute passed through condenser tube packed with 80 g Sulfolene and an approximately equal amount of glass fractionation column packing material. Maintained at a temperature of 29.5°C by circulating water from a thermostatically controlled water bath, through the condenser jacket.

DOSE ATMOSPHERE ANALYSIS

- Air saturated
- Method for the continuous analysis of sulfolene/air mixtures was not available, evidence of saturation obtained from the tendency of condensation to occur in the cooler parts of the exposure apparatus.
- Test atmosphere was analysed for sulfur dioxide and isopropyl alcohol continuously throughout the exposure period using a MIRAN 1 infra-red gas analyser. The latter was calibrated in a closed recycle loop system into which known amounts of sulphur dioxide and isopropyl alcohol were introduced using a microlitre syringe. A separate check for the sulphur dioxide content of the test atmosphere was made using chemical indicator tubes.

EXPOSURE DURATION: 4 hours

CONTROL GROUP

- 10 male and 10 female rats were housed in hanging stainless steel mesh cages throughout the duration of the experiment.
- Control group was used only for the determination of body weights and was not submitted for pathological examination.

POST DOSE OBSERVATION:

- Observed daily for toxic signs over 14 days following exposure.
- Body weights were recorded in the week prior to exposure and 14 days post exposure.

Reliability : (1) valid without restriction
Flag : Critical study for SIDS endpoint

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5.1.3 ACUTE DERMAL TOXICITY**5.1.4 ACUTE TOXICITY, OTHER ROUTES****5.2.1 SKIN IRRITATION**

Species : rabbit
Concentration : undiluted
Exposure : Occlusive
Exposure time : 24 hour(s)
Number of animals : 6
PDII : 0
Result : not irritating
EC classification : not irritating
Method : other
Year : 1982
GLP : no data
Test substance : other TS

Method : Comparable to OECD 404 - Acute Dermal Irritation/Corrosion

Result : No erythema, edema, or other dermal effects were noted at 24 or 72 hours after administration of Sulfolene. The primary irritation score is calculated to be zero.

Source : Phillips Petroleum Company Primary Skin Irritation Study in Rabbits - Sulfolene - Final Report. Study performed by Hazleton Laboratories America Inc., Vienna Virginia.

Test condition : Species: Rabbit
Strain: New Zealand White/ Dutchland
Number/Sex: Three adult males and three adult females
Housing: Housed individually
Environment: temperatures maintained at 70 +/- 4 deg F with a relative humidity of 40-60%. A 12 hour light-dark cycle was maintained.

Test Description:

- Six albino rabbits clipped free of hair
- Test material administered to one abraded site and one intact site on the back of each animal with the sites rotated over various areas of the clipped skin.
- Dose (0.5 g) applied undiluted (moistened with physiological saline before application)
- 0.5 g of solid test material introduced at each application site under a 1 inch to 1-1/2 inch square guaze patch, secured with transparant tape.
- Entire trunk of the animal wrapped with a non-absorbent binder and the animal was immobilized in a stock for 24 hours.
- After 24 hours exposure, patches were removed and the skin was wiped to remove any test substance still remaining.

Observation of Animals: The skin reactions were evaluated at 24 and 72 hours following the initial application of test material.

Scoring:

- Erythema and Eschar Formation:

No erythema ---> 0
 Very slight erythema (barely perceptible) ---> 1
 Well-defined erythema ---> 2
 Moderate to severe erythema ---> 3
 Severe erythema (beet redness) to slight eschar formation (injuries in depth) ---> 4

- Edema Formation:

No edema ---> 0
 Very slight edema ---> 1
 Slight edema (edges of area well-defined by definite raising) ---> 2
 Moderate edema (raised approximately 1 mm) ---> 3
 Severe edema (raised more than 1 mm and extending beyond the area of exposure) ---> 4

The primary skin irritation score is calculated by dividing the sum (8 values) of the erythema and edema means at 24 and 72 hours for the abraded and intact skin sites by four.

Test substance : Sulfolene (2,5-dihydrothiophene 1,1-dioxide) -- no data on purity.
Reliability : (2) valid with restrictions
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5.2.2 EYE IRRITATION

Species : rabbit
Concentration : other: normal saline slurry
Dose : 100 other: mg
Exposure Time :
Comment : not rinsed
Number of animals : 6
Result : irritating
EC classification :
Method : other
Year : 1983
GLP : no data
Test substance : other TS

Result : The mean results are presented in the following format:
 Observation / 1 hr / 24 hr / 48 hr / 72 hr / 4 days / 7 days

Cornea / 5.8 / 19.2 / 19.2 / 15.0 / 14.2 / 5.8

Iris / 1.7 / 4.2 / 4.2 / 2.5 / 1.7 / 1.7

Conjunctivae / 9.3 / 12.3 / 13.0 / 11.7 / 9.7 / 4.3

Total Score / 16.8 / 35.7 / 36.3 / 29.2 / 25.5 / 11.8

Corneal opacity, involving up to 100% of the cornea, was noted in three rabbits throughout the study and in three additional rabbits from twenty-four hours postinstillation to Day 4. Iritis was noted in five rabbits by one or twenty-four hours postinstillation. Conjunctival redness (vessels definitely injected above normal to diffuse beefy red), conjunctival chemosis (swelling above normal to swelling with lids about half closed), and conjunctival discharge (any amount above normal to moistening of the lids and hairs, and considerable area around the eye) were noted in all six rabbits. Phonation upon instillation of the test material was noted in one rabbit. Ocular irritation was present in all six rabbits at termination of the study.

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Source : Phillips Petroleum Company Unwashed Primary Eye Irritation Study in Rabbits - Sulfolene - Final Report. Study performed by Hazleton Laboratories America Inc., Vienna Virginia.

Test condition : Species: Rabbit
Strain: New Zealand White/ Dutchland
Number/Sex: Six young adult animals per group
Housing: Housed individually
Environment: temperatures maintained at 70 +/- 4 deg F with a relative humidity of 40-60%. A 12 hour light-dark cycle was maintained.

Test Description:

- The left eye of six albino rabbits were examined 24-72 hours prior to instillation of the test materials with fluorescein dye solution. Animals showing corneal damage were not used.
- Dose: 0.1 ml undiluted test material for liquids, 100 mg sample as a normal saline slurry for solids or pastes.
- Treated eyes were held closed for one second following instillation and were not washed.
- The untreated right eye of each rabbit served as a control.

Observation of Animals:

- Ocular reactions were evaluated at 24, 48, and 72 hours, and at 4 and 7 days after treatment.
- Scoring was done according to the Draize system of scoring.
- Fluorescein Staining was done after the reading at 24 hours. The eyes of the rabbits were examined with fluorescein dye solution. Any corneal damage was reconfirmed by examination with fluorescein dye solution at subsequent readings.
- The treated eye of each animal was re-examined at the termination of the study using the fluorescein dye solution to confirm the absence or presence of any corneal damage.
- Body weights were determined initially and terminally.
- The study was terminated on the seventh day, all rabbits were sacrificed with T-61.

Test substance : Sulfolene (2,5-dihydrothiophene 1,1-dioxide) -- no data on purity.
Reliability : (2) valid with restrictions
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Species : rabbit
Concentration : other: normal saline slurry
Dose : 100 other: mg
Exposure Time :
Comment :
Number of animals : 6
Result : irritating
EC classification :
Method : other
Year : 1983
GLP : no data
Test substance : other TS

Result : The mean results are presented in the following format:
Observation / 1 hr / 24 hr / 48 hr / 72 hr / 4 days / 7 days

Cornea / 20.0 / 4.2 / 5.8 / 3.3 / 3.3 / 1.7

Iris / 2.5 / 1.7 / 0.8 / 0.8 / 0.8 / 0.0

Conjunctivae / 11.7 / 7.7 / 8.3 / 4.7 / 3.3 / 2.7

Total Score / 34.2 / 13.5 / 15.0 / 8.8 / 7.5 / 4.3

Corneal opacity, involving up to 100% of the eye, was noted in all six rabbits by one hour postinstillation of Sulfolene. Corneal opacity persisted to a lesser degree in one rabbit each to twenty-four hours, seventy-two hours, and Day 4 and reoccurred in one rabbit at forty-eight hours to termination. Iritis was noted in five rabbits at varying intervals during the study. Conjunctival redness (vessels definitely injected above normal to diffuse beefy red), conjunctival chemosis (swelling above normal to obvious swelling with partial eversion of the lids), and conjunctival discharge (any amount above normal to moistening of the lids and hairs, and considerable area around the eye) were noted in all six rabbits. Phonation upon instillation of the test material was noted in one rabbit. Ocular irritation was present in five rabbits at termination of the study.

Source : Phillips Petroleum Company Washed Primary Eye Irritation Study in Rabbits - Sulfolene - Final Report. Study performed by Hazleton Laboratories America Inc., Vienna Virginia.

Test condition : Species: Rabbit
Strain: New Zealand White/ Dutchland
Number/Sex: Six young adult animals per group
Housing: Housed individually
Environment: temperatures maintained at 70 +/- 4 deg F with a relative humidity of 40-60%. A 12 hour light-dark cycle was maintained.

Test Description:

- The left eye of six albino rabbits were examined 24-72 hours prior to instillation of the test materials with fluorescein dye solution. Animals showing corneal damage were not used.
- Dose: 0.1 ml undiluted test material for liquids, 100 mg sample as a normal saline slurry for solids or pastes.
- Dosed in the conjunctival sac of the left eye of each test animal.
- Treated eyes were held closed for four seconds following instillation and then the eyes were washed with 40 ml of tap water.
- The untreated right eye of each rabbit served as a control.

Observation of Animals:

- Ocular reactions were evaluated at 24, 48, and 72 hours, and at 4 and 7 days after treatment.
- Scoring was done according to the Draize system of scoring.
- Fluorescein Staining was done after the reading at 24 hours. The eyes of the rabbits were examined with fluorescein dye solution. Any corneal damage was reconfirmed by examination with fluorescein dye solution at subsequent readings.
- The treated eye of each animal was re-examined at the termination of the study using the fluorescein dye solution to confirm the absence or presence of any corneal damage.
- Body weights were determined initially and terminally.
- The study was terminated on the seventh day, all rabbits were sacrificed with T-61.

Test substance : Sulfolene (2,5-dihydrothiophene 1,1-dioxide) -- no data on purity.

Reliability : (2) valid with restrictions

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5.3 SENSITIZATION

Type : Guinea pig maximization test
Species : guinea pig

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Concentration : Induction 40 % occlusive epicutaneous
Challenge 40 % occlusive epicutaneous

Number of animals : 40
Vehicle : other: acetone
Result : not sensitizing
Classification : not sensitizing
Method : other
Year : 1982
GLP : no data
Test substance : other TS

Result : Mortality and Clinical Observations: No deaths occurred and all animals appeared normal throughout the study.

Dermal Responses:

- Guinea pigs treated with 0.1% DNCB in acetone during the challenge phase only exhibited no dermal irritation at 24, 48, or 72 hours. Animals exposed to the same challenge concentration of DNCB, following the induction with 0.25% DNCB in acetone and a rest period, exhibited very slight to moderate to severe erythema at 24 hours and persisted to some degree to 48 and 72 hours in several animals. Comparison of these dermal responses indicate that the guinea pigs responded to hypersensitization when a known sensitizer was used.
- Guinea pigs receiving the test material, 40% sulfolene in acetone, during the challenge phase only and those animals exposed to the same challenge dose following the induction with 40% sulfolene in acetone and rest period exhibited no dermal irritation at 24, 48, or 72 hours.

Based on this response, sulfolene is not considered a dermal sensitizer in guinea pigs.

Source : Phillips Petroleum Company Dermal Sensitization Study in Guinea Pigs - Sulfolene - Final Report. Study performed by Hazleton Laboratories America Inc., Vienna Virginia.

Test condition : Species: Guinea Pig
Strain: Hartley from Dutchland Laboratory Animals, Inc.
Number/Sex: 20 males and 20 females
Age at Initiation: Adult, 300-500 grams
Housing: Housed individually
Environment: temperatures maintained at 70 +/- 4 deg F with a relative humidity of 40-60%. A 12 hour light-dark cycle was maintained.

Test Description:

- Group 1 (Positive control) - 10 animals, induction and challenge with dinitrochlorobenzene (DNCB)
- Group 2 - 10 animals, induction and challenge with 40% sulfolene
- Group 3 (Positive control) - 10 animals, challenge only with DNCB
- Group 4 (Controls) - 10 animals, challenge only with 40% sulfolene

Determination of Induction and Challenge Levels:

- Number: 4
 - Site per animal: 4
 - Induction Phase: The upper left quadrant of the backs of the guinea pigs in the test group were clipped free of hair. The following day (Day 1), 0.5 ml of test solution was applied to the shaved area near the mid line of the back and a patch (3/4" x 1" Webril Appli-Pad) held in place with Dermiclear brand transparent tape was applied. Rubber daming was wrapped around each animal to secure the patch and each pig was placed in an individual restraining device. The patches were left in place for six hours.
- Reapplication: once per week for three weeks.

---- Control Animals: no treatment
 - Challenge Phase: Two weeks following the administration of the last induction patch, the lower left quadrant of the backs of both test and control animals was shaved. The following day, 0.5 ml of the highest non-irritating dose of the test compound was applied to the shaved back for a 4 to 6 hour exposure period as performed in the induction phase.
 - Dipilation: The day following the challenge phase, the lower quadrant of each pig was dipilated with Zip by applying Zip to the area and allowing it to remain in contact with the skin for 20 to 30 minutes and then washing it off with tap water.

Observation:

- Twenty-four hours (three to five hours post dipilation), 48, and 72 hours following administration of the challenge dose.
 - The challenge sites were scored for erythema and edema according to the system of Draize.
 - After the evaluation of skin sites 72 hours following the challenge dose, all animals were sacrificed with T-61.
 - A skin section from the challenge site was fixed in 10% neutral buffered formalin, after the 72 hour challenge observation, for histopathologic evaluation.

Interpretation: No reactions greater than 1 should be seen in any of the control animals. Any reaction of grade 2 or greater on test animals that is stronger than the most severe response elicited by the controls will be considered a positive response.

Test substance : Sulfolene (2,5-dihydrothiophene 1,1-dioxide) -- no data on purity.
Reliability : (2) valid with restrictions
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5.4 REPEATED DOSE TOXICITY

Species : rat
Sex : male/female
Strain : Osborne-Mendel
Route of admin. : gavage
Exposure period : 6 weeks
Frequency of treatment : 5 consecutive days per week for 6 weeks
Post obs. period : 2 weeks
Doses : 0 (corn oil control), 56, 100, 178, 316, 562 mg/kg/day
Control group : yes, concurrent vehicle
NOAEL : = 100 - 316 mg/kg
LOAEL : = 178 - 562 mg/kg
Method : other
Year : 1978
GLP : no
Test substance : other TS

Method : Subchronic toxicity for National Cancer Institute Bioassay maximum tolerated dosages selection.

Result : ENDPOINTS EXAMINED: Mortality and weight changes.

LOAEL:

- Weight decrease: male rats = 562 mg/kg/day
 - Weight decrease: female rats = 178 mg/kg/day
 - Mortality: male rats = >562 mg/kg/day
 - Mortality: female rats = 316 mg/kg/day

NOAEL:

- Weight decrease: male rats = 316 mg/kg/day
- Weight decrease: female rats = 100 mg/kg/day
- Mortality: male rats = >562 mg/kg/day
- Mortality: female rats = 178 mg/kg/day

ADDITIONAL REMARKS: The only deaths observed among treated rats were 2 females, one receiving 316 mg/kg/d and the other receiving 562 mg/kg/d. Mean body weight depression was 17% in males treated with 562 mg/kg/d and 18% in females treated with 178 mg/kg/d. The high dosages of 3-sulfolene selected for use in the chronic bioassay were 560 mg/kg/day for male rats and 200 mg/kg/day for female rats.

Source : National Cancer Institute Carcinogenesis Technical Report Series No. 102, 1978.

Test condition : Test performed as a range-finder to determine maximum tolerated dose for a long-term carcinogenicity assay.

ANIMAL MAINTENANCE

- Rats were individually housed in suspended galvanized-steel wire-mesh cages with perforated floors in temperature- and humidity-controlled rooms.
- Temperature range was 20 - 24 deg C and the relative humidity was maintained between 45 and 55 percent.
- The air conditioning system in the laboratory provided filtered air at a rate of 12 to 15 complete changes of room air per hour.
- Fluorescent lighting was provided on a 12-hour-daily cycle.

NUMBER OF ANIMALS DOSED: Six groups, each consisting of five males and five females.

GASTRIC INTUBATION

- 3-Sulfolene mixed with corn oil was introduced by gavage to five of the six rat groups at dosages of 56, 100, 178, 316, and 562 mg/kg/day.
- The sixth group served as a control, receiving only the corn oil by gavage.
- Intubation was performed for five consecutive days per week for 6 weeks on a mg/kg body weight basis, utilizing the most recently observed group mean body weight as a guide for determining the dose.
- All animals of one sex within a treated group received the same dose.

OBSERVATION PERIOD: Two weeks after termination of dosing to detect any delayed toxicity.

Test substance : 3-Sulfolene purchased from Phillips Petroleum Company. Chemical analysis performed by Hazleton Laboratories America, Inc., Vienna, Virginia. The purity of the test chemical was indicated to be approximately 92 percent.

Reliability : (2) valid with restrictions
Flag : Critical study for SIDS endpoint
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Species : mouse
Sex : male/female
Strain : B6C3F1
Route of admin. : gavage
Exposure period : 6 weeks
Frequency of treatment : 5 consecutive days per week for 6 weeks
Post obs. period : 2 weeks
Doses : 0 (corn oil control), 316, 562, 1,000, 1,780, 3,160 mg/kg/day

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Control group : yes, concurrent vehicle
NOAEL : = 178 - 3160 mg/kg
LOAEL : = 316 - 3160 mg/kg
Method : other
Year : 1978
GLP : no data
Test substance : other TS

Method : Subchronic toxicity for National Cancer Institute Bioassay maximum tolerated dosages selection.

Result : ENDPOINTS EXAMINED: Mortality and weight changes.

LOAEL:

- Weight decrease: male mice = >3160 mg/kg/day
- Weight decrease: female mice = 316 mg/kg/day
- Mortality: male mice = 1000 mg/kg/day
- Mortality: female mice = 1000 mg/kg/day

NOAEL:

- Weight decrease: male mice = >3160 mg/kg/day
- Weight decrease: female mice = 178 mg/kg/day
- Mortality: male mice = 562 mg/kg/day
- Mortality: female mice = 562 mg/kg/day

ADDITIONAL REMARKS: No mice treated with ≤ 562 mg/kg/d died. In mice, the only group exhibiting mean body weight depression was the females receiving 316 mg/kg/d; body weight increased for all other groups receiving $\leq 1,000$ mg/kg/d relative to the controls. The high dosages of 3-sulfolene selected for use in the chronic bioassay was 450 mg/kg/day for mice of both sexes.

Source : National Cancer Institute Carcinogenesis Technical Report Series No. 102, 1978.

Test condition : Test performed as a range-finder to determine maximum tolerated dose for a long-term carcinogenicity assay.

ANIMAL MAINTENANCE

- Mice were housed by sex in groups of 10 in solid-bottom polypropylene cages equipped with filter tops in temperature- and humidity-controlled rooms.
- Temperature range was 20 - 24 deg C and the relative humidity was maintained between 45 and 55 percent.
- The air conditioning system in the laboratory provided filtered air at a rate of 12 to 15 complete changes of room air per hour.
- Fluorescent lighting was provided on a 12-hour-daily cycle.

NUMBER OF ANIMALS DOSED: Six groups, each consisting of five males and five females.

GASTRIC INTUBATION

- 3-Sulfolene mixed with corn oil was introduced by gavage to five of the six mouse groups at dosages of 316, 562, 1000, 1780, and 3160 mg/kg/day.
- The sixth group served as a control, receiving only the corn oil by gavage.
- Intubation was performed for five consecutive days per week for 6 weeks on a mg/kg body weight basis, utilizing the most recently observed group mean body weight as a guide for determining the dose.
- All animals of one sex within a treated group received the same dose.

OBSERVATION PERIOD: Two weeks after termination of dosing to detect any delayed toxicity.

5. Toxicity

Id 77-79-2

Date 23.12.2003

Test substance : 3-Sulfolene purchased from Phillips Petroleum Company. Chemical analysis performed by Hazleton Laboratories America, Inc., Vienna, Virginia. The purity of the test chemical was indicated to be approximately 92 percent.

Reliability : (2) valid with restrictions
Flag : Critical study for SIDS endpoint
26.11.2003

(24)

5.5 GENETIC TOXICITY 'IN VITRO'

Type : Mouse lymphoma assay
System of testing : Mouse lymphoma, L5178Y TK+/-, subline 3.7.2C
Concentration : 1000, 670, 449, 301, 202, 135, 90, and 61 ug/ml
Cycotoxic conc. :
Metabolic activation : with and without
Result : negative
Method : other
Year : 1982
GLP : no data
Test substance : other TS

Method : Comparable to OECD 476.

Result : SUMMARY OF MOUSE LYMPHOMA DATA FOR SULFOLENE

Results presented as Treatment & Dose Level / S-9 / % Total Survival / Mutation Frequency (x 10⁻⁵) / Fold Increase.

Media	/ - / 100.0 / 8.7 / 1.0
DMSO	/ - / 107.9 / 9.0 / -
EMS (620 ug/ml)	/ - / 25.3 / 62.0 / 7.1
1000 ug/ml	/ - / 112.6 / 9.7 / 1.1
670 ug/ml	/ - / 116.4 / 8.4 / 1.0
449 ug/ml	/ - / 142.5 / 6.6 / 0.8
301 ug/ml	/ - / 92.9 / 6.9 / 0.8
202 ug/ml	/ - / 115.6 / 6.8 / 0.8
135 ug/ml	/ - / 130.4 / 6.8 / 0.8
90 ug/ml	/ - / 79.9 / 10.6 / 1.0
61 ug/ml	/ - / 102.8 / 11.3 / 1.3
Media	/ + / 100.0 / 8.7 / 1.0
DMSO	/ + / 103.4 / 8.2 / -
MCA (3 ug/ml)	/ + / 76.0 / 19.2 / 2.2
1000 ug/ml	/ + / 57.4 / 13.1 / 1.5
670 ug/ml	/ + / 80.6 / 7.5 / 0.9
449 ug/ml	/ + / 68.6 / 10.0 / 1.1
301 ug/ml	/ + / 92.3 / 6.8 / 0.8
202 ug/ml	/ + / 90.4 / 12.4 / 1.4
135 ug/ml	/ + / 77.2 / 12.3 / 1.4
90 ug/ml	/ + / 73.8 / 13.6 / 1.6
61 ug/ml	/ + / 60.5 / 10.0 / 1.1

DMSO = Dimethylsulfoxide
EMS = Etylmethanesulfonate
MCA = 3-Methylcholanthrene

MUTAGENICITY EVALUATION

Exposure to 8 graded doses of Sulfolene, in the presence of and in the

5. Toxicity

Id 77-79-2

Date 23.12.2003

absence of metabolic activation did not increase the induction of forward mutations in L5178Y Mouse Lymphoma cells at the T/K locus.

Sulfolene is considered not to be mutagenic in this test system. (author)

Source : Phillips Petroleum Company Mouse Lymphoma Forward Mutation Assay - Sulfolene - Final Report. Study performed by Hazleton Laboratories America Inc., Vienna Virginia.

Test condition : TEST DESIGN
Six million preclensed TK +/- cells in six ml of F[10P] were added to each of 22 sterile, screw cap, 50 ml centrifuge tubes. An additional four ml of F[10P] were added to 11 of the tubes, and 4 ml of the S-9 mix were added to the remaining 11 tubes. Immediately thereafter, 0.1 ml of the 100X concentrations of the test chemical dilutions and the positive controls, and 0.1 ml of the solvent were added to the appropriate tubes. Each tube was mixed, gassed with a mixture of CO₂ and air, and incubated at 37 +/- 0.5 deg C on a revolving roller drum for four hours. Following this, incubation tubes were centrifuged and treatment solutions decanted. Cells were washed twice with F[10P] and resuspended in 20 ml F[10P] after the second wash. The tube cultures were then gassed and reincubated as described above for a two day expression time. Growth of the cells were monitored at one and two days post-exposure and the cultures readjusted to 3.0 x10⁵ cells/ml as necessary.

At the end of the expression period, a sample from each of the cultures was centrifuged, and the cells resuspended at 500,000 viable cells/ml in F[10P]. The concentrated cells were serially diluted and appropriate dilutions plated in triplicate in cloning medium with and without TFT. Approximately 500,000 viable cells (as determined by the exclusion of trypan blue) were plated on each of three selective medium plates containing 2 g/ml TFT, and 100 cells cloned on each of three non-selective plates for each test and control tube. The plates were incubated for 12 +/- 2 days. The mutant colonies (TK-/-) were counted on the selective TFT-containing plates and the survivors (TK +/- and TK-/-) were counted on the non-selective medium plates.

ACTIVATION: By an Aroclor-induced rat liver microsomal fraction

POSITIVE AND NEGATIVE CONTROLS

- Without Activation

Negative: Medium, Dimethylsulfoxide

Positive: Ethylmethanesulfonate

- With Activation

Negative: Medium, Dimethylsulfoxide

Positive: 3-Methylcholanthrene

Test substance : Sulfolene (2,5-dihydrothiophene 1,1-dioxide) -- no data on purity, assumed 100% (Hazleton); Solubility was 100 mg/ml in cell culture medium.

Reliability : (1) valid without restriction
Flag : Critical study for SIDS endpoint
20.11.2003

(11)

Type : Salmonella typhimurium reverse mutation assay
System of testing : Strains: 1535, 1537, 1538, TA98, and TA100
Concentration : 10,000; 3,333.3; 1,111.1; 370.4; and 123.5 ug/plate
Cycotoxic conc. :
Metabolic activation : with and without
Result : negative
Method : other
Year : 1982

5. Toxicity

Id 77-79-2
Date 23.12.2003

GLP : no data
Test substance : other TS
Method : Comparable to OECD 471.
Result : Number of Revertants/Plate Following Exposure to Graded Doses of Sulfolene With and Without Metabolic Activation (Number of his+ revertants per plate, three replicate assay plates):

With Metabolic Activation:

- Negative Controls

(Strain / Organism / DMSO / DGDH₂O)

1535 / 34, 14, 18 / 26, 22, 19 / 25, 30, 18

1537 / 5, 9, 6 / 7, 8, 8 / 9, 6, 5

1538 / 7, 16, 22 / 6, 13, 13 / 17, 18, 11

TA98 / 19, 14, 11 / 15, 17, 14 / 17, 19, 15

TA100 / 134, 100, 118 / 85, 107, 101 / 99, 124, 100

- Positive Controls

(Strain / MMNG [5 ug/plate] / 2-NF [50 ug/plate] / 9-AA [75 ug/plate])

1535 / 2060, 1855, 2063 / - / -

1537 / - / - / 623, 576, 708

1538 / - / 1340, 1476, 1300 / -

TA98 / - / 1641, 1708, 1630 / -

TA100 / 1871, 1997, 2067 / - / -

- 10,000 µg/plate

TA1535 - 28, 33, 31

TA 1537 - 9, 7, 8

TA1538 - 18, 18, 13

TA98 - 20, 18, 22

TA100 - 85, 125, 120

- 3,333.3 µg/plate

TA1535 - 24, 27, 35

TA 1537 - 9, 8, 6

TA1538 - 11, 24, 13

TA98 - 15, 33, 20

TA100 - 104, 96, 106

- 1,111.1 µg/plate

TA1535 - 24, 44, 23

TA 1537 - 11, 6, 9

TA1538 - 15, 8, 15

TA98 - 27, 16, 18

TA100 - 131, 104, 96

- 370.4 µg/plate

TA1535 - 31, 27, 30

TA 1537 - 11, 7, 8

TA1538 - 15, 10, 16

TA98 - 31, 20, 23

TA100 - 136, 132, 139

- 123.5 µg/plate

TA1535 - 24, 39, 22

TA 1537 - 5, 9, 7

TA1538 - 22, 8, 24

TA98 - 36, 18, 30

TA100 - 114, 118, 107

Without Metabolic Activation:

- Negative Controls

(Strain / Organism / Organism + S-9 / DMSO / DGDH2O

1535 / 34, 14, 18 / 17, 16, 14 / 9, 18, 9 / 9, 9, 8

1537 / 5, 9, 6 / 11, 5, 13 / 4, 7, 12 / 8, 6, 13

1538 / 7, 16, 22 / 26, 17, 33 / 24, 28, 30 / 12, 16, 19

TA98 / 19, 14, 11 / 30, 27, 29 / 29, 28, 24 / 26, 31, 30

TA100 / 134, 100, 118 / 125, 107, 115 / 126, 124, 95 / 107, 115, 145

- Positive Controls (ug/plate)

Strain 2-AA (5)

1535 403, 419, 367

1537 239, 220, 216

1538 1592, 1687, 1638

TA98 1715, 1860, 1741

TA100 1995, 1820, 1837

- 10,000 µg/plate

TA1535 - 14, 15, 15

TA 1537 - 8, 11, 7

TA1538 - 22, 18, 24

TA98 - 29, 28, 28

TA100 - 125, 105, 107

- 3,333.3 µg/plate

TA1535 - 17, 18, 12

TA 1537 - 6, 11, 6

TA1538 - 31, 25, 38

TA98 - 24, 22, 27

TA100 - 120, 118, 108

- 1,111.1 µg/plate

TA1535 - 10, 18, 17

TA 1537 - 11, 7, 11

TA1538 - 26, 24, 30

TA98 - 36, 35, 26

TA100 - 96, 102, 90

- 370.4 µg/plate

TA1535 - 10, 14, 20

TA 1537 - 6, 13, 9

TA1538 - 27, 24, 28

TA98 - 34, 24, 37

TA100 - 96, 115, 99

- 123.5 µg/plate

TA1535 - 12, 13, 20

TA 1537 - 16, 10, 9

TA1538 - 35, 27, 38

TA98 - 33, 28, 29

TA100 - 90, 103, 104

GENOTOXIC EFFECTS:

Negative with and without metabolic activation.

Source : Phillips Petroleum Company Salmonella typhimurium Mammalian Microsome Plate Incorporation Assay - Sulfolene - Final Report. Study performed by Hazleton Laboratories America Inc., Vienna Virginia

Test condition : TEST DESIGN
- 5 concentrations tested in triplicate.

5. Toxicity

Id 77-79-2

Date 23.12.2003

- Added to 2ml of complete top agar:
 - 0.1 ml test or control substance
 - 0.1 ml overnight broth culture of each tester strain
 - 0.5 ml S9 mix (for activated portion)
- Mixed and plated on VBE minimal agar plates.
- Allowed to harden for 1 hour.
- 2 days incubation at 37 ± 0.5 °C.
- Counted using electronic colony counter, density of background growth noted.

NUMBER OF REPLICATES: three plates per dose

FREQUENCY OF DOSING: One dose evaluated after 2 days

POSITIVE AND NEGATIVE CONTROLS

- Without Metabolic Activation
 - Negative: Organism, DMSO, DGDH2O
 - Positive: MNNG (5), 2-NF (50), 9-AA (75)
- With Metabolic Activation
 - Negative: Organism, Organism + S-9, DMSO, DGDH2O
 - Positive: 2-AA (5)

SOLVENT: dimethylsulfoxide

METABOLIC ACTIVATION: Aroclor-induced rat liver microsomal fraction.

Test substance : Sulfolene (2,5-dihydrothiophene 1,1-dioxide) -- no data on purity, assumed 100% (Hazleton); Solubility: A homogeneous suspension containing approximately 100 mg/ml was achieved in dimethylsulfoxide.

Reliability : (1) valid without restriction
Flag : Critical study for SIDS endpoint
20.11.2003

(13)

Type : Sister chromatid exchange assay
System of testing : Chinese Hamster Ovary Cells, CCL61
Concentration : 1000, 334, 100, 34, 10 ug/ml
Cycotoxic conc. :
Metabolic activation : with and without
Result : negative
Method : other
Year : 1983
GLP : no data
Test substance : other TS

Method : Comparable to OECD 479.

Result : SUMMARY OF SISTER CHROMATID EXCHANGE DATA

Without Activation -- Cells (50 cells analyzed per treatment/dose).
- Results presented as Treatment & Dose Level / Total SCE's / Number of SCE's per Cell / P Value / Fold Increase in SCE's per Cell:

Media / 310 / 6.20 / - / -
H2O / 369 / 7.38 / - / -
EMS (400 ug/ml) / 953 / 19.06 / 0.0000(S) / 2.6
Sulfolene
1000 ug/ml / 296 / 5.92 / NS / 0.8
334 ug/ml / 284 / 5.68 / NS / 0.8
100 ug/ml / 329 / 6.58 / 0.06(NS) / 0.9
34 ug/ml / 374 / 7.48 / 0.43(NS) / 1.0
10 ug/ml / 328 / 6.56 / 0.06(NS) / 0.9

Without Activation -- Chromosomes

- Results presented as Treatment & Dose Level / # Analyzed / Number of SCE's per Chromosome / P Value / Fold Increase in SCE's per Chromosome:

Media / 987 / 0.32 / - / -
H2O / 997 / 0.37 / - / -
EMS (400 ug/ml) / 992 / 0.96 / 0.0000(S) / 2.6
Sulfolene
1000 ug/ml / 988 / 0.30 / NS / 0.8
334 ug/ml / 990 / 0.29 / NS / 0.8
100 ug/ml / 987 / 0.33 / 0.07(NS) / 0.9
34 ug/ml / 997 / 0.38 / 0.44(NS) / 1.0
10 ug/ml / 995 / 0.33 / 0.08(NS) / 0.9

With Activation -- Cells (50 cells analyzed per treatment/dose).

- Results presented as Treatment & Dose Level / Total SCE's / Number of SCE's per Cell / P Value / Fold Increase in SCE's per Cell:

Media / 419 / 8.38 / - / -
H2O / 410 / 8.20 / - / -
CP (1.4 ug/ml) / 906 / 18.12 / 0.0000(S) / 2.2
Sulfolene
1000 ug/ml / 323 / 6.46 / NS / 0.8
334 ug/ml / 307 / 6.14 / NS / 0.7
100 ug/ml / 390 / 7.80 / 0.26(NS) / 1.0
34 ug/ml / 363 / 7.26 / 0.04(NS) / 0.9
10 ug/ml / 397 / 7.94 / 0.32(NS) / 1.0

With Activation -- Chromosomes

- Results presented as Treatment & Dose Level / # Analyzed / Number of SCE's per Chromosome / P Value / Fold Increase in SCE's per Chromosome:

Media / 1011 / 0.42 / - / -
H2O / 985 / 0.42 / - / -
CP (1.4 ug/ml) / 1001 / 0.90 / 0.0000(S) / 2.1
Sulfolene
1000 ug/ml / 979 / 0.33 / NS / 0.8
334 ug/ml / 987 / 0.31 / NS / 0.7
100 ug/ml / 985 / 0.40 / 0.26(NS) / 1.0
34 ug/ml / 980 / 0.37 / 0.04(NS) / 0.9
10 ug/ml / 996 / 0.40 / 0.25(NS) / 1.0

EMS = Ethylmethanesulfonate

CP = Cyclophosphamide

NS = Not significant

S = Significant

MUTAGENICITY EVALUATION:

Following exposure to five graded doses of Sulfolene, no statistically significant increase in the number of SCEs per chromosome was seen at any dose level in the presence or in the absence of metabolic activation.

Sulfolene is considered not to be mutagenic in this test system. (author)

Source : Phillips Petroleum Company In vitro Sister Chromatid Exchange Chinese Hamster Ovary Cells - Sulfolene - Final Report. Study performed by Hazleton Laboratories America Inc., Vienna Virginia.

Test condition : TEST DESIGN
- Nonactivation:

Cells treated in an exponential stage of growth by setting up cultures with 5x10⁵ cells per 25 cm² flask, 24 hours prior to treatment. Cells exposed to chemical for two hours, washed twice and 5-bromodeoxyuridine (BrdU) was added to each culture. All cultures were wrapped in aluminum foil to exclude light. Cells were sampled 24 hours after addition of BrdU to ensure completion of two full cell cycles. Duplicate cultures were set up for dose level and all controls.

- Activation:

Twenty-four hours after the initiation of cultures as described above, cells were treated with the chemical in the presence of a S-9 rat liver activation system for two hours, and washed twice in saline. From this point on, cells were sampled and treated as described for the nonactivation system.

- Colecemid Administration:

Two hours prior to fixation, colecemid (0.2 g/ml) was added to each tube.

NUMBER OF REPLICATES: 2

FREQUENCY OF DOSING: exposed for two hours

POSITIVE AND NEGATIVE CONTROLS

- Without Activation

Positive: Ethylmethanesulfonate

Negative: Media Control, H₂O

- With Activation

Positive: Cyclophosphamine

Negative: Media Control, H₂O

EVALUATION: Fifty cells in the metaphase stage of mitosis scored at each dose level for the number of sister chromatid exchanges (SCEs). Results presented as number of SCEs per cell, and SCEs per chromosome.

Test substance : Sulfolene (2,5-dihydrothiophene 1,1-dioxide) -- no data on purity, assumed 100% (Hazleton); Solubility: Repeated vortexing was required to maintain a 200 mg/ml solution in glass distilled, deionized H₂O.

Reliability : (1) valid without restriction
Flag : Critical study for SIDS endpoint
 26.11.2003

(10)

Type : Chromosomal aberration test
System of testing : Chinese hamster ovary cells
Concentration : 0, 368, 1110, and 3680 ug/ml
Cytotoxic conc. :
Metabolic activation : with and without
Result : negative
Method : other
Year : 1990
GLP : no data
Test substance : other TS

Method : Comparable to OECD Guideline 473 - "Genetic Toxicology: In vitro Mammalian Cytogenetic Test"

Result : Results are presented as Dose (ug/ml) / Number of Cells / Total % Cells with Aberrations

Without Activation - Test Material
 0 / 200 / 3
 368 / 200 / 2
 1110 / 200 / 0

3680 / 200 / 1

Without Activation - Positive Control

1 / 200 / 12

5 / 50 / 20

With Activation - Test Material

0 / 200 / 2

368 / 200 / 0

1110 / 200 / 0

3680 / 200 / 1

With Activation - Positive Control

50 / 50 / 36

Results for Sulfolene were negative both with and without activation.

Source : Loveday et al., 1990.

Test condition : Cell Culture and Medium:

- CHO cells obtained from Litton Bionetics at their fifth passage level after cloning. Cells were designated CHO-LB. - Vials were stored at -80 deg C.
- Cells were not used beyond the fifteenth passage after cloning.
- Cells were tested regularly for mycoplasma contamination using 4'-diamidino-2-phenylindole (DAPI) fluorescence and were found to be free of mycoplasma for all experiments.
- Stocks of CHO cells were maintained at 37 deg C in McCoy's 5A (modified) medium buffered with 20 mM HEPES and supplemented with 10% fetal bovine serum, 2 mM L-glutamine, 50 IU/ml penicillin, and 50 ug/ml streptomycin.
- Test cultures were set up in 75 cm² flasks 24 hr before treatment at a uniform cell density to ensure treatment of exponentially growing cultures.

Metabolic Activation

- The rat liver microsomal fraction (S9) was prepared from Aroclor 1254-induced male Sprague-Dawley rats and was combined with cofactors and culture medium to form the metabolic activation system.

Test Chemicals:

- All test chemicals were supplied as coded aliquots by the NTP chemical repository. 3-Sulfolene was supplied by Phillips Petroleum, Chemical Division.

Controls:

- Medium and solvent controls were used with each assay. Solvent controls consisted of culture medium with or without S9 and contained the same concentration of solvent as the test cultures (0.5 or 1%).
- Positive Controls: Mitomycin C (MMC) was used in the experiments without metabolic activation, and cyclophosphamide (CP) was used in the experiments with activation.
- A single CP dose of 50 ug/ml was used in the test with S9 and an MMC dose of 5 ug/ml was used in the test without S9, these doses induced aberrations in approximately 50% of the cells.

Test Description:

- Approximately 24 hr before chemical treatment, cultures were initiated at a density of 1.75E+6/flask.
- In the trials without S9, the cultures were treated with the test chemical in medium for 8 hr, washed to remove the test chemical, and treated with colcemid (10E-6 M) for 2 to 2.5 hr before cell harvest.
- In the experiments with activation, cultures were exposed to the test chemical in serum-free medium with S9 and cofactors for 2 hr, washed to

remove the test chemical and S9, and incubated at 37 deg C with fresh medium for 8 hr. Colcemid was then added, and the cells were harvested 2 hr later.

Staining and Scoring of Slides:

- Slides were stained in 5% Giemsa for 5 min.
- 200 cells per dose were scored.
- Cells were analyzed for the following categories of chromosomal aberrations:
 - "simple" - defined as a chromatid gap, break, fragment, and deletion or chromosome gap, break, or double minutes;
 - "complex" - defined as interstitial deletions, triradials, quadriradials, rings, and dicentric chromosomes; and
 - "other" - defined as pulverized chromosomes or cells with greater than 10 aberrations.
- Chromatid and chromosome gaps were recorded but were not used in the analysis.
- The frequency of polyploid or endoreduplicated cells was noted only when it seemed excessive; however, these categories were not included in the totals or in the statistical analyses.

Statistical Analysis:

- All categories of aberrations (simple, complex, and other) were combined for the statistical analysis, which was based on the percent of total cells with aberrations. The percent of aberrant cells was used for the analysis, rather than the average number of aberrations per cell.
- A binomial sampling assumption as described by Margolin et al. (1983) was used to examine absolute increased in AB's over solvent control levels at each dose. The P values were adjusted by Dunnett's method to take into account the multiple dose comparisons.
- A positive response was defined as one for which the adjusted P value was <0.05.

Test substance : 3-Sulfolene (CAS Number 77-79-2) provided by Phillips Petroleum, Chemical Div. Purity not given.

Reliability : (2) valid with restrictions
Flag : Critical study for SIDS endpoint
 23.12.2003

(18) (19)

5.6 GENETIC TOXICITY 'IN VITRO'

5.7 CARCINOGENITY

Species : rat
Sex : male/female
Strain : Osborne-Mendel
Route of admin. : gavage
Exposure period : 60 to 78 weeks
Frequency of treatment : Five consecutive days per week
Post. obs. period : 33 weeks
Doses : Males: 0, 197, and 372 mg/kg/day (time-weighted average)
 Females: 0, 120, and 240 mg/kg/day (time-weighted average)
Result : negative
Control group : yes, concurrent vehicle
Method : other
Year : 1978

5. Toxicity

Id 77-79-2
Date 23.12.2003

GLP : no
Test substance : other TS

Method : Route of Administration: gastric intubation

Duration of Test: 91 - 111 weeks

Doses/Concentration levels in rats:

- Each treatment group had 50 males, 50 females
- 3 sulfolene mixed in corn oil
- Males: 0 (corn oil control), 197, and 372 mg/kg/day (time-weighted average)
- Females: 0 (corn oil control), 120, and 240 mg/kg/day (time-weighted average)

Sex: male and female

Exposure Period: 60 - 78 weeks

Frequency of Treatment: five consecutive days per week

Control Group and Treatment:

- Corn oil by gavage and untreated control
- 20 males, 20 females in each control

Post exposure observation period: 33 weeks (rats)

Statistical Methods: Probabilities of survival were estimated by the product-limit procedure of Kaplan and Meier (1958). Statistical analyses for possible dose-related effects on survival used the method of Cox (1972) when testing two groups for equality and used Tarone's (1975) extension of Cox's methods when testing a dose-related trend. The Cochran-Armitage test for linear trend in proportions with continuity correction (Armitage, 1971) and the Fisher exact test (Cox, 1970) were used to analyze potential relationships between dose and tumor formation. Life-table methods were used to analyze the incidence of tumors. Curves of the proportion surviving without an observed tumor were computed as in Saffiotti et al. (1972).

Endpoints Examined: Mortality, weight changes, pathology/tumor incidence

Remark : Administration of 3 sulfolene via gastric intubation to Osborne-Mendel rats resulted in early mortality, which was associated with the occurrence of a variety of non-neoplastic lesions. Neoplasms that were observed occurred in incidences that were within or below the range of spontaneous incidence observed in Osborne-Mendel rats.

Under the conditions of this bioassay, there was no evidence for the carcinogenicity of 3 sulfolene to Osborne-Mendel rats.

Result : LOAEL (LOEL):
- Weight decrease: male rats = 372 mg/kg/day; weight decrease not observed in female rats
- Mortality: male rats = 197 mg/kg/day; female rats = 240 mg/kg/day

NOAEL (NOEL)

- Weight decrease: male rats = 197 mg/kg/day; female rats = 240 mg/kg/day
- Mortality: male rats = <197 mg/kg/day; female rats = 120 mg/kg/day

Statistical results:

- For male rats, the Tarone test indicated a significant ($P < 0.001$) positive

5. Toxicity

Id 77-79-2

Date 23.12.2003

association between dosage and mortality when dosed groups were compared to the vehicle controls. Due to the accelerated mortality in the high dose group, the departure from linear trend was also significant ($P < 0.001$).

- For female rats, the Tarone test showed a significant ($P = 0.002$) positive association between dosage and mortality when dosed groups were compared to the vehicle controls. The Cochran-Armitage test indicated a significant ($P = 0.029$) negative association between dose and the incidence of pituitary chromophobe adenomas; the Fisher exact test was not significant for this type of tumor.

Remarks for results: Evidence of toxicity that led to accelerated mortality was morphologically reflected primarily in the circulatory, urinary, biliary, and reproductive systems.

Source : National Cancer Institute Carcinogenesis Technical Report Series No. 102, 1978.

Test substance : 3-Sulfolene (NCI number C04557), CAS Number 77-79-2, 92% purity.

Reliability : (2) valid with restrictions
19.12.2003 (1) (3) (4) (16) (22) (23) (24)

Species : mouse
Sex : male/female
Strain : B6C3F1
Route of admin. : gavage
Exposure period : 60-78 weeks
Frequency of treatment : five consecutive days per week
Post. obs. period : 13 weeks
Doses : Males: 0 (corn oil control), 311, and 622 mg/kg/day (time-weighted average)
Females: 0 (corn oil control), 384, and 768 mg/kg/day (time-weighted average)

Result : negative
Control group : yes, concurrent vehicle
Method : other
Year : 1978
GLP : no
Test substance : other TS

Method : Route of Administration: gastric intubation

Duration of Test: 91 - 111 weeks

Doses/Concentration levels in mice:

- Each treatment group had 50 males, 50 females
- 3 sulfolene mixed in corn oil
- Males: 0 (corn oil control), 311, and 622 mg/kg/day (time-weighted average)
- Females: 0 (corn oil control), 384, and 768 mg/kg/day (time-weighted average)

Sex: male and female

Exposure Period: 60 - 78 weeks

Frequency of Treatment: five consecutive days per week

Control Group and Treatment:

- Corn oil by gavage and untreated control
- 20 males, 20 females in each control

Post exposure observation period: 13 weeks (mice)

Statistical Methods: Probabilities of survival were estimated by the product-limit procedure of Kaplan and Meier (1958). Statistical analyses for possible dose-related effects on survival used the method of Cox (1972) when testing two groups for equality and used Tarone's (1975) extension of Cox's methods when testing a dose-related trend. The Cochran-Armitage test for linear trend in proportions with continuity correction (Armitage, 1971) and the Fisher exact test (Cox, 1970) were used to analyze potential relationships between dose and tumor formation. Life-table methods were used to analyze the incidence of tumors. Curves of the proportion surviving without an observed tumor were computed as in Saffiotti et al. (1972).

Endpoints Examined: Mortality, weight changes, pathology/tumor incidence

Remark

- : The administration of the high dose of 3 sulfolene increased mortality in mice of both sexes, thus the potential carcinogenic effect could not be evaluated in these groups. Survival of animals receiving low doses was believed to be sufficient to conclude that there was no tumorigenic effect at that concentration.

Under the conditions of this bioassay, there was no evidence for the carcinogenicity of 3 sulfolene to B6C3F1 mice.

Result

- : LOAEL (LOEL):
- Weight decrease: not observed in male and female mice
 - Mortality: male mice = 622 mg/kg/d; female mice = 240 mg/kg/d

NOAEL (NOEL):

- Weight decrease: male mice = 622 mg/kg/day; female mice = 768 mg/kg/d
- Mortality: male mice = 311 mg/kg/d; female mice = 120 mg/kg/d

Statistical results:

- For male mice, the Tarone test indicated a significant ($P < 0.001$) positive association between dosage and mortality when comparing the dosed group to the vehicle control. Due to the accelerated mortality in the high dose group, the departure from linear trend was also significant ($P < 0.001$). The Cochran-Armitage test indicated a significant ($P = 0.040$) positive association between dose and incidence of hepatocellular carcinomas; the Fisher exact test was not significant.
- For female mice, the Tarone test showed a significant ($P < 0.001$) positive association between dosage and mortality when comparing the dosed groups to the vehicle control. The accelerated mortality in the high dose group resulted in significant ($P < 0.001$) departure from linear trend.

Remarks for results: Evidence of toxicity that led to accelerated mortality was morphologically reflected primarily in the circulatory, urinary, biliary, and reproductive systems.

Source

- : National Cancer Institute Carcinogenesis Technical Report Series No. 102, 1978.

Reliability
19.12.2003

- : (2) valid with restrictions

(1) (3) (4) (16) (22) (23) (24)

5.8 TOXICITY TO REPRODUCTION

5.9 DEVELOPMENTAL TOXICITY/TERATOGENICITY

5.10 OTHER RELEVANT INFORMATION

5.11 EXPERIENCE WITH HUMAN EXPOSURE

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Id 77-79-2

Date 23.12.2003

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7.1 END POINT SUMMARY

7.2 HAZARD SUMMARY

7.3 RISK ASSESSMENT

201-15167B2

Appendix II

Sulfolane Robust Summaries

RECEIVED
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Existing Chemical : Sulfolane
CAS No. : 126-33-0
EINECS Name :
EC No. :
Molecular Formula : C₄H₈O₂S

Producer related part
Company :
Creation date :

Substance related part
Company :
Creation date :

Status :
Memo :

Printing date :
Revision date :
Date of last update :

Number of pages :

Chapter (profile) :
Reliability (profile) :
Flags (profile) :

3.1.1 PHOTODEGRADATION

Type	: air
Light source	:
Light spect.	: nm
Rel. intensity	: based on Intensity of Sunlight
Indirect photolysis	
Sensitizer	: OH
Conc. of sens.	: 1.5×10^6 OH/cm ³
Rate constant	: $= 1.32785 \times 10^{-11}$ cm ³ /(molecule*sec)
Degradation	: = 50 % after 9.7 hour(s)
Deg. Product	:
Method	: other (calculated)
Year	: 2002
GLP	: no
Test substance	: no data
Method	: Calculated by using AOPWIN (ver.1.90), based on the Atkinson model recommended in the OECD Guidance.
Conclusion	: The substance in air is indirectly photodegraded with half-life of 9.7 hours.
Reliability	: (2) valid with restrictions The value is estimated with the method recommended in the OECD Guidance.
Flag	: Critical study for SIDS endpoint
18.07.2001	(b)

3.1.2 STABILITY IN WATER

Type	: abiotic
t1/2 pH4	: at degree C
t1/2 pH7	: at degree C
t1/2 pH9	: at degree C
Deg. Product	:
Method	: OECD Guide-line 111 "Hydrolysis as a Function of pH"
Year	: 1999
GLP	: No
Result	: Nominal: ca.1000 mg/L Degradation: No hydrolysis at pH 4,7 and 9 at 50±1°C for 5 days.
Test substance	: other TS; Produced by Nacalai Tesque Inc., Lot No. M6E9460, Purity: 99.6%
Conclusion	: The substance is very stable at pH4, 7 and 9 at 50±1°C for 5 days.
Reliability	: (1) valid without restriction The data is approved by the Japanese government.
Flag	: Critical study for SIDS endpoint
18.07.2001	(a)

3.1.3 STABILITY IN SOIL

3.2 MONITORING DATA**3.3.1 TRANSPORT BETWEEN ENVIRONMENTAL COMPARTMENTS**

Type : fugacity model Mackay level III
Media :
Air (level I) :
Water (level I) :
Soil (level I) :
Biota (level II / III) :
Soil (level II / III) :
Method :
Year : 2002
Method : The parameters used are shown in Appendix I .
Result : Estimated Distribution under three emission scenarios

Compartment	Release			
	100% to air	100% to water	100% to soil	equally to each compartment
Air	0.3%	0.0%	0.0%	0.1%
Water	50.7%	99.6%	45.2%	59.0%
Soil	48.8%	0.0%	54.6%	40.7%
Sediment	0.2%	0.4%	0.2%	0.2%

Attached doc. : Appendix: Parameters used in calculation of distribution by Mackay level III fugacity model.
Conclusion : The majority of the substance would distribute into water if released to aquatic compartment, and water and soil if released into air or soil and if released equally to each compartment.
Reliability : (1) valid without restriction
 The model employed is developed by the Japanese government.
Flag : Critical study for SIDS endpoint
 18.07.2001

(c)

Appendix 1 : Parameters used in calculation of distribution by Mackay level III fugacity model.

Physico-chemical parameter

molecular weight	120.17	Measured
melting point [°C]	27	Measured
vapor pressure [Pa]	1.30E+00	Measured
water solubility [g/m ³]	100000	Measured
log Kow	-0.77	Measured
half life [h] (Note 1)	in air	9.7
	in water	240000
	in soil	240000
	in sediment	720000

Temp. [°C]	25
------------	----

Environmental parameter

		volume [m ³]	depth [m]	area [m ²]	organic carbon [—]	lipid content [—]	density [kg/m ³]	residence time [h]
bulk air	air	1.0E+13					1.2	100
	particles	2.0E+03						
	total	1.0E+13	1000	1E+10				
bulk water	water	2.0E+10					1000	1000
	particles	1.0E+06			0.04		1500	
	fish	2.0E+05				0.05	1000	
	total	2.0E+10	10	2E+09				
bulk soil	air	3.2E+08					1.2	
	water	4.8E+08					1000	
	solid	8.0E+08			0.04		2400	
	total	1.6E+09	0.2	8E+09				
bulk sediment	water	8.0E+07					1000	
	solid	2.0E+07			0.06		2400	50000
	total	1.0E+08	0.05	2E+09				

Intermedia Transport Parameters [m/h]

air side air-water MTC	5	soil air boundary layer MTC	5
water side air water MTC	0.05	sediment-water MTC	1E-04
rain rate	1E-04	sediment deposition	5E-07
aerosol deposition	6E-10	sediment resuspension	2E-07
soil air phase diffusion MTC	0.02	soil water runoff	5E-05
soil water phase diffusion MTC	1E-05	soil solid runoff	1E-08

(Note 1) The half life in air is estimated by using AOPWIN (ver.1.90).

The default values applied for other half lives, as recommended by Chemicals Evaluation and Research Institute, Japan.

3.3.2 DISTRIBUTION**3.4 MODE OF DEGRADATION IN ACTUAL USE****3.5 BIODEGRADATION**

Type	: aerobic
Inoculum	: activated sludge
Concentration	: 100mg/L related to test substance
Contact time	: 14days
Degradation	: =10%after 14 days
Result	: Under test conditions no biodegradation observed
Control substance	: Aniline
Kinetic	:
Deg. Product	: Not measured
Method	: OECD Guide-line 301 C“Ready Biodegradability: Modified MITI Test(I)
Year	: 1975
GLP	: No
Result	: 10% after 14 days(based on BOD)
Test substance	: Other TS
Conclusion	: The substance is not readily biodegradable.
Reliability	: (1)valid without restriction The data is approved by the Japanese government.
Flag	: Critical study for SIDS endpoint
18.07.2001	

d

3.6 BOD5, COD OR BOD5/COD RATIO**3.7 BIOACCUMULATION**

Species	: <i>Cyprinus carpio</i> (Fish, fresh water)			
Exposure period	: 6 weeks at 25°C			
Concentration	: Yes			
Elimination	: No			
Method	: OECD Guide-line 305 E“Bioaccumulation: Flow-through Fish Test“			
Year	: 1977			
GLP	: No			
Test substance	:			
Remark	:			
Result	: Bioconcentration Factor:			

Exposure conc.	2 week	3 week	4 week	6week

2.5 mg/L	0.7, 0.6	0.6, 0.5	0.8, 0.5	0.4, 0.4
0.25 mg/L	<13, <13	<13, <13	<13, <13	<13, <13

Test condition	: Test concentrations: 2.5 mg/L and 0.25 mg/L The stock solution (10,000 mg/L) for exposure was prepared by dissolving the test substance in water. The exposure was conducted under flow-through conditions.			

Test substance : Other TS

Conclusion : The BCF of the chemical is 0.4-0.8(2.5mg/L)and <13(0.25mg/L).

Reliability : (1)valid without restriction
The data is approved by the Japanese government.

Flag : Critical study for SIDS end point
18.07.2001

e

3.8 ADDITIONAL REMARKS

4.1 ACUTE/PROLONGED TOXICITY TO FISH

Type : semistatic
Species : *Oryzias latipes* (Fish, fresh water)
Exposure period : 96 hour(s)
Analytical monitoring : yes
LC0 : ≥ 100 mg/L
LC50 : > 100 mg/L
LC100 : > 100 mg/L
Method : OECD Guide-line 203 "Fish, Acute Toxicity Test"
Year : 1999
GLP : yes
Test substance : other TS; Produced by Wako Pure Chemical Industries, Ltd. Lot No. PAH5988, Purity: 95.8%

Method : -Test organisms:
 a) Size (scaled body length and body weight): 1.8-2.0 cm, 0.083-0.12 g (n=10)
 b) Age: not described
 c) Pretreatment: Acclimated for more than 12 days at the same conditions of the test
 d) Supplier/Source: Nakajima Aquaculture (Kumamoto Prefecture, Japan)
 -Test conditions:
 a) Dilution water source: Dechlorinated tap water
 b) Dilution water chemistry: hardness=52.0 mg/L as CaCO₃, pH=7.5
 c) Exposure vessel type: 3 L volume glass aquarium (16 cm in diameter x 17 cm depth) with a lid
 d) Nominal concentrations: 0, 100 mg/L (Limit test)
 e) Vehicle/solvent and concentrations: Not used
 f) Stock solutions preparations and stability: Appropriate amount of test substance was dissolved with dilution water and 10,000 mg/L stock solution was prepared. Test solution was prepared by mixing appropriate amount of the stock solution and dilution water.
 g) Number of replicates: 2
 h) Individuals per replicates: 5
 i) Loading: Approximately 4.5 L of water was used for 1 g of fish
 j) Dosing rate, flow-through rate:
 k) Renewal frequency of test water: Semistatic with 48 hours interval
 l) Water temperature: 24±1°C
 m) Light condition: 16 hours light/8 hours dark (room light)
 n) feeding: no
 -Method of analytical monitoring: GC (at start and just before renewal of test water)
 -Statistical method:
 a) Data analysis: Binomial method
 b) Method of calculating mean measured concentrations: Time-weighted mean

Result : -Measured concentrations:

Nominal concentration (mg/L)	Measured concentration (mg/L) (Percent of nominal)		
	0-hour(a)	48-hour(b)	Mean(c)
control	n.d.	n.d.	—
100	97.8 (97.8)	103 (103)	100 (100)

n.d.: <10.0mg/L

(a) fresh solution, (b) expired solution

(c) The values are expressed as time-weighted means.

-Water chemistry in test: Water temperature=24.2-24.8°C, pH=7.2-7.3, DO=6.9-8.3 mg/L

-Cumulative mortality:

Nominal concentration (mg/L)	Cumulative number of dead fish (Percent mortality)			
	24-hour	48-hour	72-hour	96-hour
control	0(0)	0(0)	0(0)	0(0)
100	0(0)	0(0)	0(0)	0(0)

Reliability

- Statistical result: 96-hour LC₅₀ >100 mg/L.
 : (1) valid without restriction
 The data is approved by the Japanese government.
 : Critical study for SIDS endpoint

Flag

14.09.2001

f

4.2 ACUTE TOXICITY TO AQUATIC INVERTEBRATES

- Type** : static
Endpoint : Immobility
Species : *Daphnia magna* (Crustacea)
Exposure period : 48 hour(s)
Analytical monitoring : yes
NOEC : 171 mg/L
EC₅₀ : 852 mg/L
Method : OECD Guide-line 202, part 1 "Daphnia sp., Acute Immobilisation Test"
Year : 1999
GLP : yes
Test substance : other TS; Produced by Wako Pure Chemical Industries, Ltd. Lot No. PAH5988, Purity: 95.8%

Method

- : -Test organisms:
 a) Age: <24 hours after hatch
 b) Pretreatment:
 c) Supplier/Source: Laboratory cultures maintained at Chemical Inspection and Testing Institute, Japan
 -Test conditions:
 a) Dilution water source: Dechlorinated tap water
 b) Dilution water chemistry: hardness=52.0 mg/L as CaCO₃, pH=7.5
 c) Exposure vessel type: Petri dish (8.5 cm diameter x 5.7 cm depth)
 d) Nominal concentrations: 0, 95.3, 171, 309, 556, 1000 mg/L
 e) Vehicle/solvent and concentrations: Not used
 f) Stock solutions preparations and stability: Appropriate amount of test substance was dissolved with dilution water and 10,000 mg/L stock solution was prepared. Test solution was prepared by mixing appropriate amount of the stock solution and dilution water and divided into 4 vessels.
 g) Number of replicates: 4
 h) Individuals per replicates: 5
 i) Volume of test solution: 200mL/vessel
 j) Renewal rate of test water: no
 k) Water temperature: 20±1°C
 l) Light condition: 16 hours light/8 hours dark (room light intensity)
 m) feeding: no
 -Method of analytical monitoring: GC (at start and end of test)
 -Statistical method:

a) Data analysis: Probit methods
b) Method of calculating mean measured concentrations: Time-weighted mean

Result : -Measured concentrations

Nominal concentration (mg/L)	Measured concentration (mg/L) (Percent of nominal)		
	0-hour(a)	48-hour(b)	Mean(c)
control	n.d.	n.d.	—
95.3	94.3(99.0)	91.6 (96.2)	93.0 (97.6)
171	164(95.6)	161(93.9)	162(94.8)
309	315(102)	285(92.2)	300(97.0)
556	528(95.0)	531(95.4)	529(95.2)
1,000	1,010(101)	936(93.6)	972(97.2)

n.d.: <10.0 mg/L

(a) fresh solution, (b) expired solution

(c) The values are expressed as time-weighted means.

-Water chemistry in test: Water temperature=20.2-20.5°C, pH=7.8-7.9,
DO=8.7-8.8 mg/L

-Cumulative immobilization:

Nominal concentration (mg/L)	Cumulative number of Immobilized Daphnia (Percent immobility)	
	24-hour	48-hour
control	0 (0)	0(0)
95.3	0 (0)	0 (0)
171	0 (0)	0 (0)
309	0 (0)	1 (5)
556	3 (15)	3 (15)
1,000	12 (60)	13 (65)

The values include dead Daphnia.

-Statistical result: 24 and 48-hour EC₅₀=889 and 852 mg/L

Reliability : (1) valid without restriction
The data is approved by the Japanese government.

Flag : Critical study for SIDS endpoint

14.09.2001

g

4.3 TOXICITY TO AQUATIC PLANTS E.G. ALGAE

Species : *Selenastrum capricornutum* (Algae)
Endpoint : Biomass and growth rate
Exposure period : 72 hour(s)
Analytical monitoring : yes
NOEC (biomass) : 171 mg/L
NOEC (growth rate) : 309 mg/L (24-48h)
EC₅₀ (biomass) : 500 mg/L
EC₅₀ (growth rate) : >1,000 mg/L
Method : OECD Guide-line 201 "Algae, Growth Inhibition Test"
Year : 1999

- GLP** : yes
- Test substance** : other TS; Produced by Wako Pure Chemical Industries, Ltd.
Lot No.PAH5988,Purity: 95.8%
- Method** :
- Test organisms:
 - a) Supplier/Source (strain number): Laboratory cultures maintained at Chemical Inspection and Testing Institute, Japan/ATCC 22662
 - b) Preculture (duration, medium, etc.): 3 days under the same method of test in OECD medium
 - Test conditions:
 - a) Test medium: OECD medium
 - b) Exposure vessel type: 500 mL volume glass Erlenmeyer flask
 - c) Nominal concentrations: 0, 95.3, 171, 309, 556, 1000 mg/L
 - d) Vehicle/Solvent and concentrations: not used
 - e) Stock solutions preparations and stability: Appropriate amount of test substance was dissolved with OECD medium and 10,000 mg/L stock solution was prepared. The stock solution was sterilized by filtration with 0.45 µm membrane filter. Test solution was prepared by mixing appropriate amount of the stock solution and OECD medium.
 - f) Number of replicates: 3
 - g) Initial cell number (initial biomass): 1×10^4 per mL
 - h) Volume of test solution: 100mL/vessel
 - i) Water temperature range: $23 \pm 2^\circ\text{C}$
 - j) Light condition (intensity, duration): 4000-5000 lux, continuous
 - Method of analytical monitoring: GC (at start: test solution from another vessel for analysis, and at end: Centrifuged supernatant of mixed test solution from 3 test vessels)
 - Statistical method:
 - a) Data analysis: Comparison of areas under the growth curves and growth rate. NOEC: one-way ANOVA and Dunnett's multiple comparison. EC_{50} : method of least squares
 - b) Method of calculating mean measured concentrations: Time-weighted mean

Result : -Measured concentrations

Nominal concentration (mg/L)	Measured concentration (mg/L) (Percent of nominal)		
	0-hour(a)	72-hour(b)	Mean(c)
control	n.d.	n.d.	—
95.3	97.5(102)	93.9 (98.5)	95.7 (100)
171	171(99.9)	165(96.5)	168(98.2)
309	303(98.0)	305(98.7)	304(98.4)
556	565(102)	537(96.5)	551(99.0)
1,000	976(97.6)	916(91.6)	946(94.6)

n.d.:<10.0mg/L

(a)initial, (b) final

(c)The values are expressed as time-weighted means.

-Water chemistry in test: Water temperature= $22.5\text{--}24.9^\circ\text{C}$, pH= $7.9\text{--}8.0$ at the initiation of exposure and $8.6\text{--}9.9$ at the termination of exposure

-Cell concentration at each flask of each measuring point:

Nominal Concentration (mg/L)	Cell density ($\times 10^4$ cells/mL)				
	No.	0-hour	24-hour	48-hour	72-hour
Control	1	1.0	6.6	48.3	208.6
	2	1.0	5.5	47.2	199.9

	3	1.0	6.7	57.0	242.1
	Average	1.0	6.3	50.8	216.9
	S.D	0.0	0.6	5.4	22.3
95.3	1	1.0	6.4	49.4	221.4
	2	1.0	4.9	47.5	223.5
	3	1.0	6.1	48.8	177.8
	Average	1.0	5.8	48.5	207.6
	S.D	0.0	0.8	1.0	25.8
171	1	1.0	5.5	39.0	163.9
	2	1.0	4.9	39.7	187.0
	3	1.0	5.4	41.2	183.8
	Average	1.0	5.3	40.0	178.2
	S.D	0.0	0.3	1.1	12.5
309	1	1.0	5.5	42.5	186.5
	2	1.0	5.5	30.6	103.1
	3	1.0	5.6	34.3	147.9
	Average	1.0	5.5	35.8	145.8
	S.D	0.0	0.1	6.1	41.8
556	1	1.0	5.0	16.3	90.1
	2	1.0	4.3	21.0	102.5
	3	1.0	5.4	25.1	111.5
	Average	1.0	4.9	20.8	101.4
	S.D	0.0	0.5	4.4	10.7
1,000	1	1.0	4.5	20.5	82.6
	2	1.0	5.1	13.9	46.9
	3	1.0	4.4	13.1	45.4
	Average	1.0	4.7	15.8	58.3
	S.D	0.0	0.3	4.0	21.1

-Growth inhibition:

Nominal Concentration (mg/L)	Area No.	Area (X10E+4) 0-72h	Inhibition (%) 0-72h	Rate 24-48h	Inhibition (%) 24-48h	Rate 24-72h	Inhibition (%) 24-72h
Control	1	3760	-	0.0831	-	0.0720	-
	2	3600	-	0.0893	-	0.0747	-
	3	4370	-	0.0894	-	0.0748	-
	Average	3910	-	0.0873	-	0.0739	-
95.3	1	3940	-0.608	0.0853	2.22	0.0739	-0.0610
	2	3880	0.849	0.0944	-8.19	0.0795	-7.61
	3	3390	13.3	0.0866	0.752	0.0703	4.90
	Average	3740	4.52	0.0888	-1.74	0.0746	-0.923
171	1	2970	24.0	0.0819	6.16	0.0709	4.08
	2	3260	16.8	0.0870	0.343	0.0758	-2.55

	3	3260	16.6	0.0846	3.12	0.0734	0.595
	Average	3170	19.1	0.0845	3.21	0.0734	0.708
309	1	3330	14.9	0.0856	1.94	0.0736	0.364
	2	2040	47.8	0.0715	18.1	0.0611	17.3
	3	2670	31.7	0.0757	13.3	0.0683	7.59
	Average	2680	31.4	0.0776	11.1	0.0676	8.43
556	1	1530	60.8	0.0493	43.5	0.0603	18.3
	2	1780	54.6	0.0657	24.7	0.0659	10.8
	3	2010	48.6	0.0643	26.3	0.0632	14.5
	Average	1770	54.7	0.0598	31.5	0.0631	14.5
1,000	1	1530	60.8	0.0628	28.1	0.0604	18.2
	2	960	75.5	0.0421	51.8	0.0463	37.3
	3	906	76.8	0.0451	48.3	0.0484	34.4
	Average	1130	71.1	0.0500	42.7	0.0517	30.0

The control group showed normal growth (more than 200-fold increase after 72hr). The growth was inhibited at 1,000 mg/L, 556 mg/L and 0.640 mg/L. The lower concentration groups showed similar growth to the control.

-Statistical result: EbC₅₀(0-72 h)= 500 mg/L (95% confidence limits: 416 – 601 mg/L) and NOEbC=171 mg/L.

ErC₅₀(24-48 h) >1,000 mg/L and NOECr(24-48h)=309mg/L. ErC₅₀(24-72 h) >1,000 mg/L and NOErC(24-72h)=556 mg/L.

Reliability : (1) valid without restriction
The data is approved by the Japanese government.

Flag : Critical study for SIDS endpoint

14.09.2001

h

4.4 TOXICITY TO MICROORGANISMS E.G. BACTERIA

4.5.1 CHRONIC TOXICITY TO FISH

4.5.2 CHRONIC TOXICITY TO AQUATIC INVERTEBRATES

Species : *Daphnia magna* (Crustacea)

Endpoint : reproduction rate

Exposure period : 21 day

Analytical monitoring : yes

NOEC : 25.0 mg/L

LCEC : 50.0 mg/L

EC₅₀ : >100 mg/L

LC₅₀ : >100 mg/L

Method : OECD Guide-line 211 "Daphnia magna reproduction test" (Draft Guideline, April 1997)

Year : 1999

GLP : yes

- Test substance** : other TS; Produced by Wako Pure Chemical Industries, Ltd.
Lot No.pah5988,Purity: 95.8%
- Method** : -Test organisms:
a) Age: <24 hours after hatch
b) Pretreatment:
c) Supplier/Source: Laboratory cultures maintained at Chemical Inspection and Testing Institute, Japan
-Test conditions:
a) Dilution water source: Dechlorinated tap water
b) Dilution water chemistry: hardness=52.0 mg/L as CaCO₃, pH=7.5
c) Exposure vessel type: 100 mL volume glass beaker
d) Nominal concentrations: 0, 25.0, 50.0, 100 mg/L
e) Vehicle/solvent and concentrations: Not used
f) Stock solutions preparations and stability: Appropriate amount of test substance was dissolved with dilution water and 1000 mg/L stock solution was prepared. Test solution was prepared by mixing appropriate amount of the stock solution and dilution water and divided into 10 vessels.
g) Number of replicates: 10
h) Individuals per replicates: 1
i) Volume of test solution: 500 mL/vessel
j) Renewal frequency of test water: Semistatic with 3 times per week
k) Water temperature: 20±1°C
l) Light condition: 16 hours light/8 hours dark (room light intensity)
m) feeding: Chlorella vulgaris, 0.1-0.2 mg organic carbon/individual/day
-Method of analytical monitoring: GC (just before and after renewal of test water x 3)
-Statistical method:
a) Data analysis: Kruskal-Wallis, Dunnett multiple comparisons method for dead parental Daphnia. Kruskal-Wallis for time of the first production of young. Analysis of variance in one-way classification and Scheffe's multiple comparisons for mean cumulative numbers of young production per adult.
b) Method of calculating mean measured concentrations: Time-weighted mean

Result : -Measured concentrations:

Nominal concentration (mg/L)	Measured concentration (mg/L) (Percent of nominal)			
	0-day(a)	2-day(b)	11-day(a)	14-day(b)
control	n.d.	n.d.	n.d	n.d.
25.0	24.9(99.6)	24.3 (97.0)	24.6 (98.3)	24.2(96.6)
50.0	50.8(102)	49.1(98.2)	47.9(95.9)	51.2(102)
100	99.1(99.1)	101(101)	97.7(97.7)	103(103)

(continued)

Nominal concentration (mg/L)	Measured concentration (mg/L) (Percent of nominal)		
	16-day(a)	18-day(b)	Time-weighted mean(c)
control	n.d.	n.d.	n.d
25.0	25.6(102)	24.2(97.0)	24.6(98.3)
50.0	51.8(104)	48.8(97.6)	49.9(99.7)
100	106(106)	96.7(96.7)	101(101)

n.d.:<10.0mg/L

(a)fresh solution, (b) expired solution

(c)The values are expressed as time-weighted means.

-Water chemistry in test: Water temperature=20.0-20.3°C, pH=7.5-8.6, DO=8.3-8.8 mg/L, hardness=43.0-49.0 mg/L as CaCO₃

-Cumulative number of dead parental Daphnia:

Nominal concentration (mg/L)	Exposure time (day)			
	3	7	14	21
control	0 (0)	0 (0)	0 (0)	0 (0)
25.0	0 (0)	0 (0)	0 (0)	0 (0)
50.0	0 (0)	0 (0)	0 (0)	4 (40)
100	0 (0)	0 (0)	0 (0)	4 (40)

The values in parentheses express mortality (%) of Daphnia.

-Time of the first production of young: 8 days in all test groups

-Mean cumulative numbers of young production per adult:

Nominal concentration (mg/L)	Exposure time (day)							
	7	8	9	10	11	12	13	14
control	0	21.2	21.3	21.3	62.0	62.0	62.0	106
25.0	0	20.0	20.0	20.0	55.9	55.9	55.9	96.6
50.0	0	18.7	18.7	18.7	53.0	53.0	53.0	94.3
100	0	19.5	19.5	19.5	51.5	51.5	51.5	77.5

(continued)

Nominal concentration (mg/L)	Exposure time (day)						
	15	16	17	18	19	20	21
control	106	106	109	146	146	146	178
25.0	97.2	97.2	109	132	132	136	155
50.0	94.3	94.5	107	132	132	132	160
100	80.2	80.2	80.2	93.0	93.0	93.0	96.5

-Significant test of difference between the mean cumulative number of juveniles produced per adult in control and test vessels after 21 days exposure:

Nominal concentration (mg/L)	Vessel No.						
	1	2	3	4	5	6	7
control	184	190	185	187	169	186	183
25.0	133	136	159	196	171	180	116
50.0	-	113	186	170	176	-	172
100	106	18	-	145	-	101	115

(continued)

Nominal concentration (mg/L)	Vessel No.			Mean	S.D.	Significant difference
	8	9	10			

control	170	202	128	178	20.1	
25.0	109	185	168	155	30.1	
50.0	-	141	-	160	27.4	
100	-	94	-	97	42.4	**

**: Significantly different from Control at $p < 0.01$.

-Statistical result: 14 and 21-day LC50 for dead parental Daphnia > 100 mg/L, 14 and 21-day EC50 for reproduction > 100 mg/L, 21-day NOEC and LOEC for reproduction = 25.0 and 50.0 mg/L based on the nominal concentrations.

Reliability : (1) valid without restriction
The data is approved by the Japanese government.

Flag : Critical study for SIDS endpoint

14.09.2001

i

4.6.1 TOXICITY TO SOIL DWELLING ORGANISMS

4.6.2 TOXICITY TO TERRESTRIAL PLANTS

4.6.3 TOXICITY TO OTHER NON-MAMM. TERRESTRIAL SPECIES

4.7 BIOLOGICAL EFFECTS MONITORING

4.8 BIOTRANSFORMATION AND KINETICS

4.9 ADDITIONAL REMARKS

5.0 TOXICOKINETICS, METABOLISM AND DISTRIBUTION**5.1.1 ACUTE ORAL TOXICITY****Acute Oral Toxicity****TEST SUBSTANCE**

- Tetrahydrothiophene-1,1-dioxide (CAS No. 126-33-0)
- Remarks: Source: Produced by Shin Nippon Rika , Lot No:0007 ,Purity 95 %
(other constituent: Water 5 %)

METHOD

- **Method/guideline:** OECD Guideline 401
- **Test type:** Acute Oral Toxicity Test
- **GLP:** Yes
- **Year:** 1996 (published year)
- **Species:** Rat
- **Strain:** Crj: CD(SD)
- **Route of administration:** Oral(by single-dose gavage)
- **Dose/concentration levels:** 0, 892, 1204, 1626, 2195, 2963, 4000 mg/kg
- **Sex:** Male & Female
- **Control group and treatment:** Vehicle
- **Post exposure observation period:** 14 days
- **Statistical methods :** LD50 was calculated by Van der Waerden method

REMARKS FIELD FOR TEST CONDITIONS**Test Subjects:**

- **Age at study initiation:** 5 week old for both sexes
- **Weight at study initiation:** 122-138g for males, 107-120g for females
- **No. of animals per sex per dose:** 5 per sex per dose group

Study Design:

- **Vehicle:** Purified water

- **Satellite groups and reasons they were added:** none
- **Clinical observations performed and frequency:** Each rat was weighed immediately prior to treatment, the day and thereafter 1, 3, 7 and 14 days after treatment. The rats were observed periodically during two-week post-treatment observation period for signs of toxicity. All rats were submitted for a gross pathological examination.

RESULTS

- **LD₅₀:**
Male: 2006 mg/kg b.w. (1783-2256 mg/kg b.w., 95% confidence limit)
Female: 2130 mg/kg b.w. (1844-2460 mg/kg b.w., 95% confidence limit)

REMARKS FIELD FOR RESULTS

Body weight: Body weights of all treated group were lower than those of the control group on the day after dosing.

- **Food consumption:** Not done
-
- **Clinical signs** (description, severity, time of onset and duration): Signs of toxicity were observed at the dose group more than 1204 mg/kg, including convulsion, decreased locomotor activity, ptosis, salivation, piloerection, chromodacryorrhea and perineal region soiling with urine.
-

Decreased locomotor activity; more than 1204 mg/kg
Convulsion, ptosis, salivation, piloerection, chromodacryorrhea, perineal region soiling with urine; more than 1626 mg/kg

- **Hematology :** Not done
 - **Biochem:** Not done
 - **Ophthalmology:** Not done
- Mortality and time to death:**

Mortality of male and female rats

Dose level (mg/kg)	#Dead/ #Treated		Time of death	
	Males	Females	Males	Females
0	0/5	0/5	-	-
892	0/5	0/5	-	-
1204	0/5	0/5	-	-
1626	0/5	0/5	-	-
2195	4/5	3/5	Day 0 4/5	Day 0 3/5
2963	5/5	5/5	Day 0 5/5	Day 0 5/5
4000	5/5	5/5	Day 0 5/5	Day 0 5/5

- **Gross pathology incidence and severity:** Dead animals showed hemorrhagic black spots in their glandular stomach mucosa at necropsy.
- **Organ weight changes:** Not done
- **Histopathology (incidence and severity):** Not done

CONCLUSIONS

LD₅₀ was established at 2006 mg/kg for male and 2130 mg/kg for female, respectively.

DATA QUALITY

- **Reliabilities:** Valid without restriction

Remarks field for Data Reliability

Well conducted study, carries out by Research Institute for Animal Science in Biochemistry and Toxicology

REFERENCES(Free Text)

Ministry of Health and Welfare: Japan, Toxicity Testing Reports of Environmental Chemicals. 4, 435-436 (1996)

GENERAL REMARKS

5.1.2 ACUTE INHALATION TOXICITY

5.1.3 ACUTE DERMAL TOXICITY

5.1.4 ACUTE TOXICITY, OTHER ROUTES

5.2.1 SKIN IRRITATION

5.2.2 EYE IRRITATION

5.3 SENSITIZATION

5.4 REPEATED DOSE TOXICITY

Repeated Dose Toxicity (a)

TEST SUBSTANCE

- Tetrahydrothiophene-1,1-dioxide (CAS No. 126-33-0)
- Remarks: Source: Shinn Nippon Rika, Lot No:0007, Purity 95 % (other constituent: water 5%, Kept at 4° C until use

METHOD

- **Method/guideline:** TG for 28-day repeat dose toxicity testing of Chemicals(Japan)
- **Test type:** 28-day Repeat Dose Toxicity Test
- **GLP:** Yes
- **Year:** 1996 (published year)
- **Species:** Rat
- **Strain:** Crj: CD(SD)
- **Route of administration:** Oral(gavage)
- **Dose/concentration levels:** 0, 60, 200, 700 mg/kg/day
- **Sex:** Male & Female
- **Exposure period:** Males and females, for 28 days
- **Frequency of treatment:** Daily
- **Control group and treatment:** Concurrent vehicle
- **Post exposure observation period:** 14 days (for 0 and 700 mg/kg/day group)
- **Terminal killing:** Males and females, days 29 or 43
- **Statistical methods :** Dunnett's test
t-test and u-test for data of recovery group

REMARKS FIELD FOR TEST CONDITIONS**Test Subjects:**

- **Age at study initiation:** 5 week old for both sexes
- **Weight at study initiation:** 146-157g for male, 126-140g for female
- **No. of animals per sex per dose:** 6 per sex per dose for the group at 60, 200 mg/kg/day, and 12 per sex per dose for the group at 0, 700 mg/kg/day

Study Design:

- **Vehicle:** Purified water
- **Satellite groups and reasons they were added:** none
- **Clinical observations performed and frequency:** General condition was observed once a day. Body weight and food consumption were determined at day 1, 3 after treatment, and thereafter twice a week. Hematological and blood chemical analysis were carried out at the day 28 (all groups) and at the 43 (control and 700 mg/kg :recovery group). Urinary analysis were carried out at the day 23 (male), 24 or 27 (female) for all group, and at the day 34 (male) and 32 (female) for control and 700 mg/kg (recovery group).
- **Organs examined at necropsy:**
 - Organ weight:** brain, heart, liver, kidneys, spleen, thymus, adrenal glands, testes, epididymides, ovary
 - Microscopic:** control & all treated groups(male)/ kidney control & 700mg/kg groups/brain, spinal cord, pituitary, eye ball, thyroid, thymus, heart, trachea, lung, liver kidneys, spleen, adrenals, stomach, small intestines, pancreas, testes, epididymides, prostate, ovary, uterus, vagina, bladder, lymph node, sciatic nerve, bone marrow

RESULTS• **NOAEL**

60 mg/kg/day for males and 200 mg/kg/day for females

• **LOAEL**

Male: 200 mg/kg/day (histopathological changes in the kidney)
 Female: 700 mg/kg/day (suppression of body weight gain & food consumption, and slight increase of GPT value in blood chem.)

REMARKS FIELD FOR RESULTS

Body weight: Decrease of body weight gain in 700 mg/kg males and females

- **Food consumption:** Decrease in 700 mg/kg males and females
- **Clinical signs** (description, severity, time of onset and duration): Transient reduction of locomotor activity at the early stage in 700mg/kg females
- **Mortality and time to death:** The death was not observed in any group.
- **Hematology and biochemical findings:**
 - Male: Slight decrease in MCHC at all groups ($P<0.05$ ~ $P<0.01$), but no dose-related, and no changes in erythrocytes, hemoglobin, and hematocrit values. Increase in leukocyte at 700mg/kg of recovery group ($P<0.05$).
 - Female: Decrease in erythrocytes and increase in MCV at 700mg/kg of recovery group ($P<0.01$).

Hematology examinations in male and female rats

	28days dosing group				14 days recovery group	
Dose level(mg/kg)	0	60	200	700	0	700
No. of animals	6	6	6	6	6	6
Male						
MCHC (%)	346±0.8	338±0.4*	335±0.2**	336±0.4**	243±0.5	345±0.8
Leukocytes ($10^2/\text{mm}^3$)	60±16	58±19	58±13	64±7	76±19	104±22**
Female						
erythrocytes ($10^4/\text{mm}^3$)	773±21	778±32	752±23	778±42	817±16	781±21**
MCV (fl)	57±2	57±2	57±1	58±1	55±1	57±1**

(* $P<0.05$, ** $P<0.01$)

- **Blood chemistry:**
 - Male: Increase of cholinesterase ($P<0.05$) and total bilirubin ($P<0.01$), and decrease of chloride ($P<0.01$) at 700mg/kg
 - Female: Increase of GPT ($P<0.01$) and decrease of glucose ($P<0.05$) at 700 mg/kg

Blood chemical examinations in male and female rats

	28days dosing group				14days recovery group	
Dose level(mg/kg)	0	60	200	700	0	700
No. of animals	6	6	6	6	6	6
Male						
ChE(IU/l)	304±175	296±106	281±60	294±41*	292±81	263±47
T.bilirubin(mg/dl)	0.35±0.05	0.35±0.05	0.40±0.05	0.45±0.03**	0.28±0.02	0.30±0.05
Cl(mEq/l)	104±0	104±1	104±1	102±1**	103±2	103±1
Female						
GPT(IU/l)	24±5	24±4	23±3	35±6**	27±6	29±5
Glucose(mg/dl)	130±15	117±13	123±10	110±4*	139±13	125±10

(* $P<0.05$, ** $P<0.01$)

- **Gross pathology incidence and severity:** Slight hypertrophy of kidney at 700 mg/kg males (2/6)
- **Organ weight changes :**
 - Male: Increase of relative weight of kidneys ($P<0.01$), brain and heart ($P<0.05$) at 700 mg/kg
 - Female: Decrease of splenic weight ($P<0.05$) at 700 mg/kg. Increase of absolute and relative weight of spleen

(P<0.01) at 700 mg/kg of recovery group

Organ weight in male and female rats

	28days dosing group				14days recovery group	
Dose level(mg/kg)	0	60	200	700	0	700
No. of animals	6	6	6	6	6	6
Male, relative weight						
Brain(g%)	0.62±0.03	0.64±0.03	0.64±0.03	0.68±0.05*	0.52±0.04	0.54±0.04
Kidneys(g%)	0.77±0.04	0.80±0.05	0.79±0.05	0.94±0.06**	0.67±0.05	0.71±0.08
Heart(g%)	0.34±0.03	0.35±0.03	0.35±0.01	0.39±0.03*	0.32±0.02	0.34±0.03
Female, absolute wt.						
Spleen(g)	0.48±0.06	0.43±0.05	0.44±0.08	0.37±0.03*	0.44±0.06	0.53±0.05*
Relative wt.						
Spleen	0.24±0.03	0.22±0.03	0.23±0.05	0.20±0.01	0.20±0.02	0.24±0.02*

(*P<0.05, **P<0.01)

- Histopathology (incidence and severity):

Male: Increase of hyaline droplets and eosinophilic bodies in the renal tubules in 200 and 700 mg/kg. Increase of basophilic renal tubules at 700 mg/kg

Female: No significant effect was observed.

CONCLUSIONS

The NOAELS are considered to be 60 mg/kg/day for males and 200 mg/kg for females.

DATA QUALITY

- **Reliabilities:** Valid without restriction

Remarks field for Data Reliability

Well conducted study, carries out by Research Institute for Animal Science in Biochemistry and Toxicology (Japan)

REFERENCES(Free Text)

Ministry of Health and Welfare: Japan, Toxicity Testing Reports of Environmental Chemicals, 4, 437-445 (1996)

GENERAL REMARKS

Repeated Dose Toxicity (b)

TEST SUBSTANCE

- Tetrahydrothiophene-1,1-dioxide (CAS No. 126-33-0)
- Remarks: Source: Produced by Sumitomo Seika Chemicals, Lot No.20802
Purity: 99.3%, kept at room temperature until use

METHOD

- **Method/guideline:** OECD TG 421
- **Test type:** OECD Preliminary Reproduction Toxicity Screening Test
- **GLP:** Yes
- **Year:** 1999(published year)
- **Species:** Rat
- **Strain:** Crj: CD(SD)IGS
- **Route of administration:** Oral(by gavage)
- **Dose/concentration levels:** 0, 60, 200, 700 mg/kg/day(in Water)
- **Sex:** Male & Female
- **Exposure period:** Male; for 49 days
Female; for 41-50 days from 14 days prior to mating to the
3 day of lactation
- **Frequency of treatment:** Daily
- **Control group and treatment:** Concurrent vehicle
- **Post exposure observation period:** none
- **Terminal killing:** Males; day 50
Females; day 4 of lactation
- **Statistical methods :** Dunnett's)following to Bartlett or Kruskal-Wallis analysis)
and Chi square test

REMARKS FIELD FOR TEST CONDITIONS**Test Subjects:**

- **Age at study initiation:** 10 week old for both sexes
- **Weight at study initiation:** 355-379g for males, 209-228g for females
- **No. of animals per sex per dose:** 12 per sex per dose group

Study Design:

- **Vehicle:** Water
- **Satellite groups and reasons they were added:** none
- **Clinical observations performed and frequency:** General condition was observed twice a day. Body weight and food consumption for males were determined twice a week, and for females, body weight and food consumption were determined twice a week prior to mating and in principle, once a week for gestation and lactation period.
- **Organs examined at necropsy:**
Organ weight: testes, epididymides, ovaries
Microscopic: control & 700 mg/kg groups/ testis, epididymides, ovary

RESULTS

- **NOAEL**

200 mg/kg/day in both sexes

- **LOAEL**

Both sexes: 700 mg/kg/day (death, clinical toxic signs, suppression of body weight gain)

REMARKS FIELD FOR RESULTS

- **Body weight:** Suppression of body weight gain was observed in the 700 mg/kg male and during pre-mating and lactation period in the 700 mg/kg female.
- **Food consumption:** Decrease in food consumption was observed in the 700 mg/kg male, and during pre-mating and lactation period in the 700 mg/kg female.
- **Clinical signs** (description, severity, time of onset and duration): Soiled fur for both sexes and soft stool for males in the 700 mg/kg group were noted.
Mortality and time to death: One male and one female in the 700 mg/kg group died.
- **Hematology and biochemical findings:** Not done

- **Gross pathology incidence and severity:** No significant effect was observed.
- **Organ weight changes :**
 - Male: No significant effect was observed.
 - Female: The relative ovary weights were increased in the 700 mg/kg group.

Ovary weights

Dose level (mg/kg)	0	60	200	700
No. of dams	12	12	12	12
Ovaries				
Relative (mg%)	32.90±4.36	33.04±4.62	34.66±3.33	40.45±5.92**

(∴P<0.01)

- **Histopathology (incidence and severity):** No significant effect was observed.

CONCLUSIONS

Toxic effects in this study are death, clinical toxic signs, suppression of body weight gain and low food consumption.

The NOAELS are considered to be 200 mg/kg/day for both sexes.

DATA QUALITY

- **Reliabilities:** Valid without restriction

Remarks field for Data Reliability

Well conducted study, carried out by Nihon Bioresearch Inc. Hashima Laboratory (Japan)

REFERENCES(Free Text)

Ministry of Health and Welfare: Japan, Toxicity Testing Reports of Environmental Chemicals, 7, 471-481 (1999)

GENERAL REMARKS

5.5 GENETIC TOXICITY 'IN VITRO'

GENETIC TOXICITY IN VITRO (BACTERIAL TEST)

TEST SUBSTANCE

- Tetrahydrothiophene-1,1-dioxide (CAS No. 126-33-0)
- Remarks: Source: Produced by Shinn Nippon Rika, Lot No.8050074 , Purity: above 99.9%, Kept at room temperature until use

METHOD

- **Method/ guideline:** Guidelines for Screening Mutagenicity Testing of Chemicals (JAPAN) and OECD Test Guideline 471 and 472
- **Test type:** Reverse mutation assay
- **GLP:** Yes
- **Year:** 1996 (published year)
- **Species/Strain:** Salmonella typhimurium TA100, TA1535, TA98, TA1537
Escherichia coli WP2uvrA
- **Metabolic activation:** S9 from rat liver, induced with phenobarbital and 5,6-benzoflavone
- **Statistical methods:** No statistic analysis

REMARKS FIELD FOR TEST CONDITIONS

Study Design:

- **Concentration:** -S9 mix: 0, 313, 625, 1250, 2500 and 5000 ug/plate
+S9 mix: 0, 313, 625, 1250, 2500 and 5000 ug/plate
- **Number of replications:** 2
- **Plates/tests:** 3
- **Procedure:** Plate incorporation method
- **Solvent:** Water for injection
- **Positive controls:** -S9 mix; 2-(2-Furyl)-3-(5-nitro-2-furyl)acrylamide(TA100, TA98, WP2), Sodium azide(TA1535) and 9-Aminoacridine (TA1537)
+S9 mix; 2-Aminoanthracene (five strains)

RESULTS

- **Cytotoxic concentration:**

Toxicity was not observed up to 5000 ug/plate in the five strains with and without S9 mix.

- **Precipitation concentration:**

Precipitation was not observed at any concentration with and without S9 mix.

- **Genotoxic effects:**

	+	?	-
With metabolic activation:	[]	[]	[X]
Without metabolic activation	[]	[]	[X]

REMARKS FIELD FOR RESULTS**CONCLUSIONS**

Bacterial gene mutation is negative with and without metabolic activation.

DATA QUALITY

- **Reliabilities:** Valid without restriction

Remarks field for Data Reliability

Well conducted study, carried out by Hatano Research Institute, Food and Drug Safety Center (Japan)

REFERENCES(Free Text)

Ministry of Health and Welfare: Japan, Toxicity Testing Reports of Environmental Chemicals, 4, 449-450 (1996)

GENERAL REMARKS

GENETIC TOXICITY IN VITRO (NON-BACTERIAL IN VITRO TEST)**TEST SUBSTANCE**

- Tetrahydrothiophene-1,1-dioxide (CAS No.126-33-0)
- Remarks: Source: Produced by Shinn Nippon Rika, Lot No.8050074
Purity: above 99.9%

METHOD

- **Method/guideline:** Guideline for Screening Mutagenicity Testing of Chemicals (Japan)
- **Test type:** Chromosome aberration test
- **GLP:** Yes
- **Year:** 1996 (published year)
- **Species/ Strain:** CHL/IU cell
- **Metabolic activation:** S9 from rat liver, induced with phenobarbital and 5,6-benzoflavone
- **Statistical methods:** Fisher's exact analysis

REMARKS FIELD FOR TEST CONDITIONS**Study Design:**

For continuous treatment, cells were treated for 24 or 48 hrs without S9 mix.
For short-term treatment, cells were treated for 6 hrs with and without S9 mix and cultivated with fresh media for 18 hrs.

- **Concentration:**
 - S9 mix(continuous treatment): 0, 0.30, 0.60, 1.2 mg/ml
 - S9 mix(short-term treatment): 0, 0.30, 0.60, 1.2 mg/ml
 - +S9 mix(short-term treatment): 0, 0.30, 0.60, 1.2 mg/ml
- **Plates/test:** 2
- **Solvent:** Water for injection
- **Positive controls:** Mitomycin C for continuous treatment
Cyclophosphamide for short-term treatment

RESULTS• **Cytotoxic concentration:**

50 % Growth inhibition was not observed at any concentration with or without S9 mix.

• **Genotoxic effects:**

	clastogenicity			polyploidy		
	+	?	-	+	?	-
With metabolic activation:	[]	[]	[X]	[]	[]	[X]
Without metabolic activation	[]	[]	[X]	[]	[]	[X]

REMARKS FIELD FOR RESULTS

Structural chromosomal aberrations and polyploidy were not induced up to a maximum concentration of 1.2 mg/ml on continuous or short-term treatment with and without an exogenous metabolic activation system, respectively.

CONCLUSIONS

Chromosomal aberration in CHL/IU cells is negative with and without metabolic activation.

DATA QUALITY

- **Reliabilities:** Valid without restriction

Remarks field for Data Reliability

Well conducted study, carried out by Hatano Research Institute, Food and Drug Safety Center (Japan)

REFERENCES(Free Text)

Ministry of Health and Welfare: Japan, Toxicity Testing Reports of Environmental Chemicals 4, 451-453 (1996)

GENERAL RENARKS**5.6 GENETIC TOXICITY 'IN VIVO'****5.7 CARCINOGENICITY**

5.8.1 TOXICITY TO FERTILITY

5.8.2 DEVELOPMENTAL TOXICITY/TERATOGENICITY

5.8.3 TOXICITY TO REPRODUCTION, OTHER STUDIES

TEST SUBSTANCE

- Tetrahydrothiophene-1,1-dioxide (CAS No. 126-33-0)
- Remarks: Source: Produced by Sumitomo Seika Chemicals, Lot No. 20802
Purity: 97.3%, kept at room temperature until use

METHOD

- Method/guideline: OECD TG 421
- Test Type: OECD Preliminary Reproduction Toxicity Screening Test
- GLP: Yes
- Year: 1999 (published year)
- Species: Rat
- Strain: Crj: CD(SD) IGS
- Route of administration: Oral (by gavage)
- Dose /concentration levels: 0, 60, 200, 700 mg/kg/day (in Water)
- Sex: Male & Female
- Exposure period: Male; for 49 days
Female; for 41-50 days from 14 days prior to mating
to the 3 day of lactation
- Frequency of treatment: Daily
- Control group and treatment: Concurrent vehicle
- Post exposure observation period: none
- Terminal killing: Males; day 50
Females; day 4 of lactation
- Statistical methods: Dunnett's (following to Bartlett or Kruskal-Wallis analysis)
and Chi square test

REMARKS FIELD FOR TEST CONDITIONS

Test Subjects:

- **Age at study initiation:** 10 week old for both sexes
- **Weight at study initiation:** 355-379 g for males, 209-225 g for females
- **No. of animals per sex per dose:** 12 per sex per dose group

Study Design:

The animals were sacrificed on the day 4 of lactation for females. Females with no copulation were killed on the final day of mating period. Females with no delivery were killed on the day 25 of pregnancy.

- **Vehicle:** Water
- **Satellite groups and reason they were added:** none
- **Mating procedure:** Male / female per cage; 1/1, length of cohabitation; at most 14 days, until proof of copulation (formation of vaginal plug or sperm detection in vagina)
- **Clinical observations performed and frequency:**
Parent: general appearance twice a day
Pups: general appearance once a day after birth
- **Organs examined at necropsy:**
Parent: organ weight: testes, epididymis, ovaries
Microscopic: control & 700 mg/kg group/ testis, epididymis, ovary
Pups: full macroscopic examinations on all pups
- **Parameters assessed during study:**
 Body weight and food consumption for males were determined twice a week, and for females, body weight and food consumption were determined twice a week prior to mating and in principle, once a week for gestation and lactation period. estrus cycle daily until successful day of copulation, No. of pairs successful copulation, copulation index (No. of pairs with successful copulation/No of pairs mated x 100), paring days until copulation, No. of pregnant females, fertility index=(No. of pregnant animals/ No. of pairs with successful copulation x 100), No. of corpora lutea, No. of implantation sites, implantation index (No. of implantation sites/No. of corpora lutea x 100), No. of living pregnant females, No. of pregnant females with parturition, gestation length, No. of pregnant females with live pups on day 0, gestation index(No. of females with live pups/No. of living pregnant females x 100), No. of pregnant females with live pups on day 4 , delivery I index(No. of pups born/ No. of implantation sites x 100), No. of pups alive on day 0 of lactation, live birth index(No. of live pups on day 0/ No. of pups born x 100), sex ratio(Total No. of male pups/ Total No. of female pups), No. of pups alive on day 4 of lactation, viability index(No. of live pups on day 4 / No. of live pups on day 0 x 100), body weight of live pups(on day 0 and 4)

RESULTS

- **NOAEL for reproductive performance:** 700 mg/kg/day for males,
200 mg/kg /day for females
- **NOAEL: pups toxicity:**
60 mg/kg/day

• **Maternal data with dose level (with NOAEL value):**

The number of estrus cases was decreased in the 700 mg/kg group. Four dams lost all their pups during lactation period in the 700 mg/kg group.

• **Pups data with dose level (with NOAEL value):**

Birth index, live birth index, number of pups on days 0 and 4 of lactation, viability index, and body weights of both sexes on days 0 and 4 of lactation were decreased, and the number of stillbirths increased in the 700 mg/kg group. Birth index and the number of pups on day 0 and 4 of lactation decreased in the 200 mg/kg group.

Reproductive parameters

Dose level(mg/kg)	0	60	200	700
No. of estrus cases(14 days)	3.3±0.5	3.3±0.5	3.2±0.4	2.2±0.9**
No. of dams	11	12	10	10
Birth index (%)	96.3±6.5	95.8±4.8	90.5±5.1*	71.6±26.2**
Dead pups on day 0	0.3±0.5	0.2±0.4	0.2±0.4	3.6±4.4**
Live birth index(%)	98.1±3.3	98.8±2.8	98.7±2.8	75.9±26.2**
Live pups on day 4	14.8±1.8	15.0±1.9	13.7±1.3	4.0±5.6**
Viability index(%)	99.5±1.8	100.0±0.0	97.3±1.3	29.2±40.4**
Body weight				
Male Day 0	6.64±0.31	6.15±0.42*	6.22±0.38	5.44±0.52**
4	9.92±0.75	9.63±1.16	9.57±1.03	6.63±1.41**(4)
Female Day 0	6.20±0.84	5.88±0.33	5.85±0.44	4.93±0.46**
4	9.25±0.84	9.19±0.96	9.18±1.31	5.68±1.37**(5)

(*P<0.05, **P<0.01)

REMARKS FIELD FOR RESULTS

- **Mortality and day of death:** One male and one female in the 700 mg/kg group died
- **General toxic signs:** Soiled fur for both sexes and soft stool for males in the 700 mg/kg group were noted.
- Body weight:** Suppression of body weight gain in males, and in females during the pre-mating period in the 700 mg/kg was observed.
- Food consumption:** Decrease of food consumption in males, and in females during the pre-mating and lactation period in the 700mg/kg was observed.
- **Pups data:** Grossly visible abnormalities : no significant effect was observed.

CONCLUSIONS

Toxic effects for female parent and pups are effects on reproductive parameters, such as decrease of the number of estrus cases and increase of dams losing all of their pups. With regards to pups, toxicity are effects on developmental parameters including number of pups, viability index, stillbirth and body weight.

The NOAELs are considered to be 200 mg/kg for maternal parents and 60 mg/kg for pups.

DATA QUALITY

- **Reliabilities:** Valid without restriction

Remarks field for Data Reliability

Well conducted study, carried out by Nihon Bioresearch Inc. Hashima Laboratory (JAPAN)

REFERENCES(Free Text)

Ministry of Health and Welfare: Japan, Toxicity Testing Reports of Environmental Chemicals 7, 471-481 (1999)

GENERAL REMARKS**5.9 SPECIFIC INVESTIGATIONS****5.10 EXPOSURE EXPERIENCE****5.11 ADDITIONAL REMARKS**

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- a METI, Japan (1999) Ministry of Economy, Trade and Industry (former MITI), Test No.80132K conducted by Chemicals Evaluation and Research Institute, Japan (former CITI , Japan) unpublished data.
 - b Sumika Technoservice Corporation (2002a)
 - c Sumika Technoservice Corporation (2002b)
 - d METI, Japan (1975) Ministry of Economy, Trade and Industry (former MITI), conducted by Chemicals Evaluation and Research Institute, Japan (former CITI , Japan) unpublished data.
 - e METI, Japan (1977) Ministry of Economy, Trade and Industry (former MITI), conducted by Chemicals Evaluation and Research Institute, Japan (former CITI , Japan) unpublished data.
 - f EA, Japan (1999), The Environment Agency, Ecotoxicology testing report (unpublished), Test No. 92060 conducted by Chemical Evaluation and Research Institute, Japan (former CITI, Japan)
 - g EA, Japan (1999), The Environment Agency, Ecotoxicology testing report (unpublished), Test No. 92058 conducted by Chemical Evaluation and Research Institute, Japan (former CITI, Japan)
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